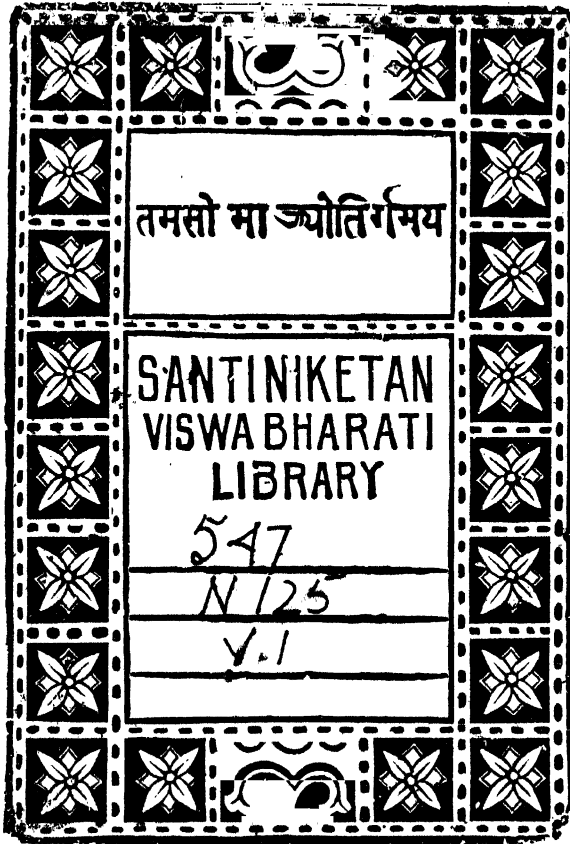


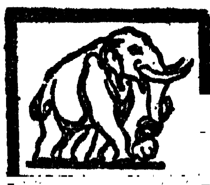
Organic Chemistry

FOR ADVANCED STUDENTS

VOLUME I
Analytical and Synthetical

PART I

by
V. V. NADKARNY
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POPULAR PRAKASHAN BOMBAY

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Dedicated to

the memory of

REV. FR. F. J. SACASA, S. J.

Principal, St. Xavier's College, 1932–1933

CONTENTS

CHAPTER I

CARBOHYDRATES

Introduction : The sugars, starches and celluloses together constitute the carbohydrates, an important non-nitrogenous group of natural products. They are very widely distributed in nature. The sweet fruits, canes, and honey, contain a large amount of the simple sugars. Another form in which some of the simple sugars, glucose, galactose and arabinose are found to occur in nature, is in combination with other molecules like alcohols and phenols to give *glycosides*. The latar occur very abundantly in nature. The blue and red colouring matters the *anthocyanins*, the yellow pigments, the *anthoxanthins* and some other physiologically important compounds ot digitalis, belong to this class. The *tannins* contain simple sugar molecules in combination with typical acids, as an ester ; the typical acids involved are the gallic and digallic acids. The starches which are more complex, form the chief constituents of rice, maize, arrowroot, and potato. The celluloses from cotton, wood, grass etc., which are the most complex of them all, are the basis of all plant structure. Of all organic compounds found in nature, cellulose seems to be the most plentiful.

The carbohydrates comprise one of the technically most important groups of natural products. They constitute the raw materials of numerous chemical industries so essential to modern civilization. The paper industry, the artificial silk, rayon and cellulose acetate industry use enormous quantities of cellulose. The latter is employed in large amounts in the manufacture of explosives. The modern big textile industry is based on it. The starch also finds extensive applications. The manufacture of commercial cheap glucose is such an important application. Large quantities of starch are fermented by the action of yeast to yield alcohol, one of the most important organic chemicals. Another important fermentation industry is the production of butyl alcohol and acetone.

Lastly carbohydrates (sugars) serve as sources of energy and starches as stores of potential energy. Plants can build up carbohydrates by photosynthesis, while animals have to rely on the plants for their supply and requirements of the carbohydrates.

General Composition and Properties. The sugars, starches and celluloses contain carbon, hydrogen and oxygen only. The empirical composition as given by the elementary analysis is expressed by the formula $(CH_2O)n$ *i.e.* hydrate of carbon. The Germans called these substances "Kohlen-hydrates" and hence the English—CARBO-HYDRATES. Many of the naturally occurring carbohydrates contain carbon atoms whose number is six or its simple multiple. Thus, we have the simple sugars, glucose, fructose with the formula $C_6H_{12}O_6$; while the starches and celluloses possess the formula $(C_6H_{10}O_5)n$. Sugars cantaining five carbon atoms with the formula $C_5H_{10}O_5$ are all known. The most common are arabinose and xylose. They occur chiefly as the polysaccharides, arabans and xylans respectively. In recent times, sugars like rhamnose and fucose have been isolated, which possess the formula $C_6H_{12}O_5$ and have been shown to be methyl sugars. Also organic compounds are known which possess the same empirical composition (CH_2O) but are not sugars *e. g.* acetic acid, lactic acid, etc. These facts, thus show the limitation of the term, carbohydrate. Hence the modern term "Glucides or Saccharides."

Classification and Nomenclature. The old classification of the substances into (a) *sugars* and (b) *nonsugars* was purely empirical, based on the molecular composition and some physical properties.

The *nonsugars* are compounds of unknown molecular weight and are insoluble, tasteless and amorphous. They possess colloidal properties associated with high molecular weight; they are called polysaccharides; functionally they belong to two different groups: (*a*) those which serve as food materials: (*b*) those which constitute the structural materials: the starches serve as reserve foods while the celluloses and gums comprise the structural materials of plants. The starches and celluloses are called polysaccharides as on acid hydrolysis, many molecules of a simple sugar are produced from one molecule of the complex nonsugar.

Starch $(C_6H_{10}O_5)n \rightarrow$ n mols of glucose.
Cellulose $(C_6H_{10}O_5)n \rightarrow$ n mols of glucose.

The gums and the pectins are closely related to polysaccharides in structure and in general behaviour, and are called polyuronides. The polyuronide molecule is built up of uronic acid molecules in the

same way as a polysaccharide is from the simple sugar. Thus alginic acid is built up of d-mannuronic acid residues. Pectin is similarly the polyuronide derived from d-galacturonic acid.

The *sugars* include the soluble sweet crystalline compounds of known molecular weight *e. g.* glucose, fructose and cane-sugar. An elaborate classification of the sugars is known which depends on the numerical relationships obtaining between the carbon atoms and H_2O molecules in the compound. Thus we have: (*a*) monosaccharides; (*b*) disaccharides and (*c*) trisaccharides.

(*i*) MONOSACCHARIDES—(The ending-ose is reserved for sugar; the ending-ide is also in use)—with the general formula $C_n(H_2O)_n$ *i. e.* the number of carbon atoms is the same as that of (H_2O) groups *e. g.* Glucose, fructose, mannose, which possess the molar formula $C_6H_{12}O_6$. Other common monosaccharoses are the pentoses, arabinose and xylose etc. with the molar composition $C_5H_{10}O_5$. They are stable toward hydrolytic agents (cannot be broken down into simple sugar).

(*ii*) DISACCHARIDES—These have the general formula $C_{2n}(H_2O)_{2n-1}$; they are built up from two molecules of the same or different monosaccharoses by the elimination of one molecule of water; they are readily hydrolysed into monosaccharoses; *two* moles of hexoses are produced.

Cane-sugar	$C_{12}H_{22}O_{11}$	$\rightarrow$ glucose and fructose
Maltose	$C_{12}H_{22}O_{11}$	$\rightarrow$ glucose and glucose
Lactose	$C_{12}H_{22}O_{11}$	$\rightarrow$ glucose and galactose.

(*iii*) TRISACCHARIDES—These give on hydrolysis three molecules of a hexose, Raffinose ($C_{18}H_{32}O_{16}$) gives a molecule each of glucose fructose and galactose.

The monosaccharides thus appear to be the building blocks of the disaccharides and also of the more complex sugars, starches and celluloses.

The di- and poly-saccharoses are also referred to as "holosides" in contra distinction to glycosides which are known as "heterosides." The glycosides on hydrolysis give a sugar and a non-sugar residue, aglycon. Oligosaccharides is still another term sometimes used for sugars containing 2–10 molecules of monosaccharides.

MONOSACCHAROSES

The most important, naturally occurring monosaccharoses are glucose, fructose, mannose and galactose which are all hexoses. Among the pentoses, arabinose, xyloses and ribose are the most common.

D-Glucose is the only aldose which occurs free in nature; *D*-mannose is obtained by the hydrolysis of *Seminine*, the reserve cellulosic material of many plants. It is also present in the shell of the ivory nut. D-Galactose is found in lactose in combination with glucose; D-fructose is present in honey, cane-sugar, inulin, dahlia root etc.

The monosaccharoses exhibit both structural isomorism and stereo-isomerism. Thus structurally, they are shown to be poly-hydroxy-aldehydes or ketones. They are classified according to (*a*) the length of the carbon chain and (*b*) the nature of carbonyl function. Thus there are pentoses, hexoses and heptoses which are further subdivided into (i) aldoses and (ii) ketoses. *Aldoses* contain the aldehydic function and the *ketoses* the ketonic function. Only 2-ketohexoses are known.

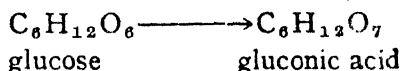
They can be further classified as (*a*) pyranoses or δ sugars and (*b*) furanoses or γ sugars.

PENTOSES	aldo-pentose *e.g.* arabinose	
HEXOSES	aldo-hexose *e.g.* glucose, mannose	
	keto-hexose *e.g.* fructose, sorbose.	
Boise	$C_2H_4O_2$	Glycollic aldehyde
Trioses	$C_3H_6O_3$	Glyceric aldehyde Dihydroxy acetone
Tetroses	$C_4H_8O_4$	Erythrose
Pentoses	$C_5H_{10}O_5$	Arabinose, ribose, xylose, lyxose are all aldoses; no ketoses are known among the pentoses.
Methyl pentose	$C_6H_{12}O_5$	Rhamnose
Hexoses	$C_6H_{12}O_6$	Glucose, mannose, galactose are all aldoses. Fructose, sorbose are the ketoses.
Heptoses	$C_7H_{14}O_7$	Gluco-heptose, mannoheptose
Octoses	$C_8H_{16}O_8$	
Nonoses	$C_9H_{18}O_9$	

Sugars rhamnose, fucose are called methyl-aldoses. They are aldoses in which the terminal CH_2OH group is replaced by CH_3 group. They possess the general formula $C_6H_{12}O_5$; they are also called *desoxy*-sugars or desoses.

General reactions of the Monosaccharoses :—The monosaccharoses possess some characteristic properties and give a few specific reactions. These reactions can be classified as (i) aldehydic, (ii) alcoholic, (iii) alcoholic-aldehydic and (iv) α glycolic A large amount of our knowledge of the structure of these compounds and their natural inter-relationships is based on these reactions.

Aldehydic Properties :—As aldehydes, the monosaccharoses readily reduce Fehling's solution (alkaline copper sulphate solution) and Tollen's reagent (ammoniacal silver nitrate solution) and Benedict's solution which is a solution of $CuSO_4$ in alkaline sodium citrate. These reactions are made the basis of methods for their detection and estimation. With bromine water, in presence of Ag_2O, $CaCO_3$, they are oxidised to monobasic acids (aldonic acids) containing the same number of carbon atoms.

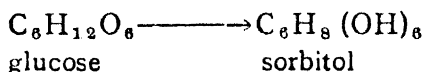


$$\underset{\text{glucose}}{C_6H_{12}O_6} \longrightarrow \underset{\text{gluconic acid}}{C_6H_{12}O_7}$$

The reaction with I_2 and NaOH, proceeds quantitatively to form the aldonic acid: this is made the basis of a method of estimating the aldoses.

Nitric acid oxidises them to dibasic acid: glucose→saccharic acid.

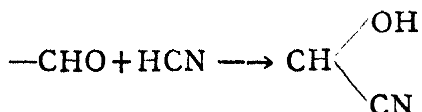
Reducing agents like sodium and alcohol, convert them into hexahydric alcohols :



$$\underset{\text{glucose}}{C_6H_{12}O_6} \longrightarrow \underset{\text{sorbitol}}{C_6H_8(OH)_6}$$

Recently, electrolytic reduction, and catalytic reduction under pressure have also been attempted.

Another reaction of the monosaccharoses is the reaction with HCN (Kiliani's reaction), the aldehydic or the ketonic group is involved and the corresponding cyanohydrins are formed :



$$-CHO + HCN \longrightarrow CH\begin{cases} OH \\ CN \end{cases}$$

This reaction has been found to be very useful analytically and synthetically. The addition of HCN is stereo-specific and it can be regarded as a case of asymmetric synthesis.

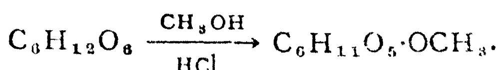
The monosaccharoses do not react with $NaHSO_3$ solution or ammonia.

Alcoholic Properties :—The alcoholic groups present in the molecule of the monosaccharoses can be *esterified*; thus acetyl and benzoyl derivatives which are crystalline compounds have been obtained.



$$C_6H_{12}O_6 \longrightarrow C_6H_7O\,(OCOCH_3)_5$$

Secondly, the hydroxy-group may be *alkylated e. g.* methylated by the action of a suitable methylating agent *e. g.* CH_3OH and HCl, CH_3I, $(CH_3)_2\,SO_4$

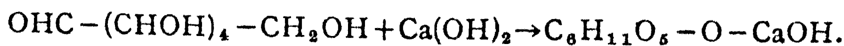


$$C_6H_{12}O_6 \xrightarrow[HCl]{CH_3OH} C_6H_{11}O_5{\cdot}OCH_3.$$

Such mono-methyl compounds are called glucosides when derived from glucose or glycosides in general. They are related to the natural glycosides in structure. The methyl sugars thus obtained by further methylation have found an important application in the structural investigations of the sugars. The preparation of the methyl sugars was studied extensively by British Chemists, the outstanding of them being Irvine, Haworth and Hirst.

Similarly acetone sugars and trityl derivatives of the sugars have been prepared. The phosphoric esters of the sugars are known to play an important role in the chemistry of muscle and fermentation processes.

Lastly, with $Ca(OH)_2$, $Ba(OH)_2$ and $Sr(OH)_2$, the corresponding alcoholates are formed. They are readily decomposed by carbon dioxide, when the original sugar is regenerated. These reactions are utilised in the refining of sugars.



$$OHC-(CHOH)_4-CH_2OH+Ca(OH)_2 \rightarrow C_6H_{11}O_5-O-CaOH.$$

Alcoholic-aldehydic Properties :—On account of the presence of $-CHOH-CHO$, or $CH_2OH-CO-$groupings sugars react with excess of phenyl hydrazine $C_6H_5NHNH_2$ in acetic acid solution in presence of small amount of $NaHSO_3$, to give "osazones." The

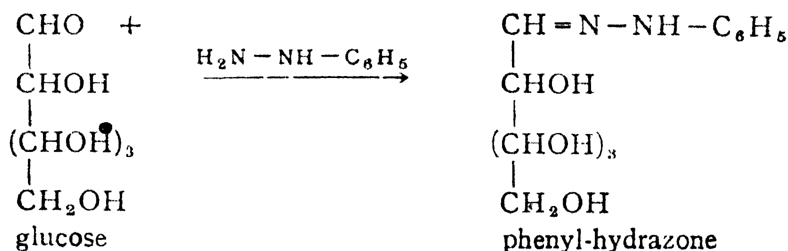
latter are sparingly soluble, characteristically well-defined crystalline compounds and possess a variable melting-point (204° 205°C); hence they find application in the separation and identification of the isomeric sugars. The rate of formation of the osazones under specific conditions of temperature and concentration is highly characteristic and is used to detect an individnal sugar. The rate of formation of the osazones from the sugars is :

Monosaccharoses	*Time in minutes*
d - Fructose	2
d - Galactose	15
d - Glucose	4–5
d - Mannose	0·5

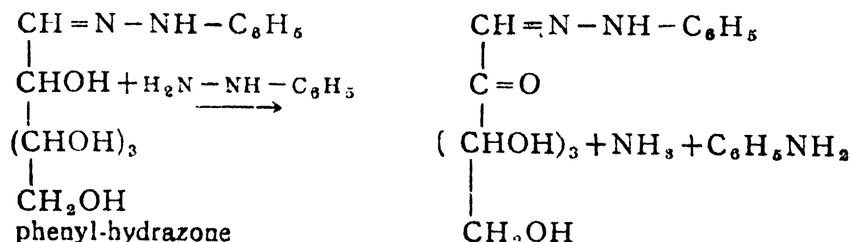
The osazones from the disaccharides are soluble in the hot water and hence do not separate out. The chemistry of the osazone formation is as follows :

The formation of osazone from a sugar which is a hydroxy aldehyde or ketone involves three distinct stages. Taking glucose as an example :

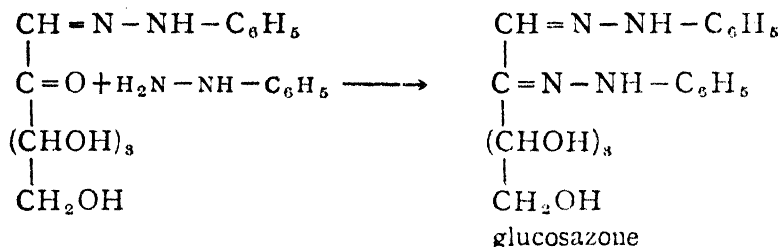
(i) THE FORMATION OF PHENYL–HYDRAZONE



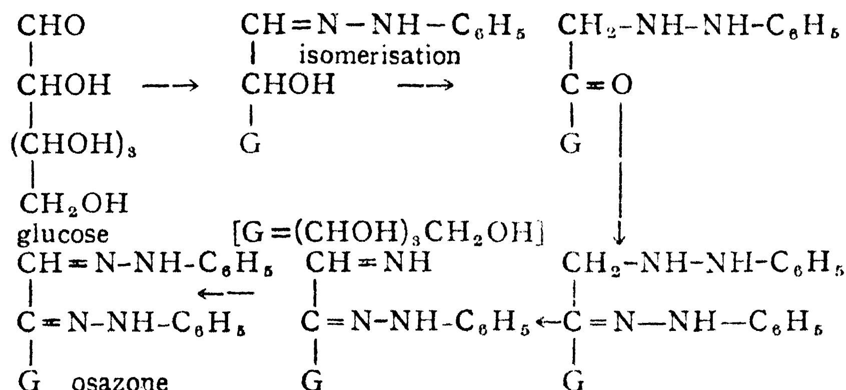
(ii) OXIDATION OF THE HYDRAZONE BY EXCESS OF PHENYL-HYDRAZINE



(iii) THE FORMATION OF THE OSAZONE (dihydrazone).



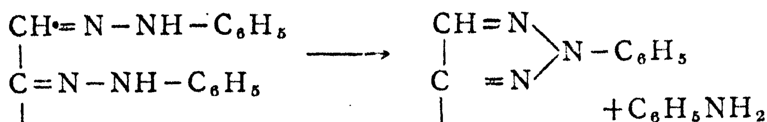
The above is Fischer's mechanism of osazone formation. It has become questionable with the realisation that phenyl-hydrazine is not reduced by $TiCl_3$ and thus does not function as an oxidising agent. Recently Weygand has proposed an alternate mechanism :



The isomerisation reaction indicated in the above mechanism is known as Amadori rearrangement. This type of acid catalysed reactions are known in other series of compounds.

This reaction of phenyl-hydrazine with sugars to give osazones, discovered and developed by E. Fischer, is one of the two simple reactions which are responsible for the great advances made in carbohydrate chemistry. The other reaction is methylation.

Recently, it has been shown by Hudson that the m. ps of the osazones are variable and they probably represent decomposition temperatures. He has therefore suggested the use of triazole derivatives for the complete characterisation of the sugars The triazole derivatives are produced when the osazones are heated with aqueous $CuSO_4$ solution.



They are called oso-triazoles ; they are readily purified, are very stable and possess sharp and characteristic melting points. The m. p. of gluco-oso triazole is 195°–6°.

α glycolic properties :—The sugars are polyhydroxy compounds and are glycolic in nature. Hence they are attacked by HIO_4 and Pb-tetra acetate. The periodic acid is soluble in water and is therefore used extensively in the investigation of structures of sugars and sugar derivatives.

The Molisch test :—The sugar solution develops a characteristic violet colouration with an α-naphthol solution in concentrated sulphuric acid. A small quantity of alcoholic solution of α-naphthol is added to a small quantity of sugar solution. Con. H_2SO_4 is then added along the side of the test tube. A violet colour is developed at the interface of the two liquids. The sugar is converted by the concentrated acid into ω-hydroxymethyl furfuraldehyde which gives the violet colour with α-naphthol.

The levulinic acid test :—With con. HCl, a hexose first gives ω-hydroxy-methyl furfural which can be further decomposed to form levulinic acid $CH_3CO{\cdot}CH_2{\cdot}CH_2COOH$. The latter can be isolated as Ag-salt (distinction from pentoses).

GENERAL METHODS OF INVESTIGATION OF STRUCTURE OF THE MONOSACCHAROSES :—The problem of the structural relationships of the sugar has been a very intriguing one. The complexity of the sugar molecules and the difficulty of their purification combined with the task of separating them from a mixture of closely related compounds presented almost insuperable practical difficulties. However, with the application of the greatest experimental talents of the great genius Emil Fischer, and his students, the structural relationships between the different sugars have been successfully unravelled. From time to time, new weapons of attack based on some typical reactions of the molecule have been forged and utilised in the elucidation of the structure. Some of the typical reactions employed will be discussed below.

The sugars contain carbon, hydrogen and oxygen only. The elucidation of the structure of such a molecule involves the deter-

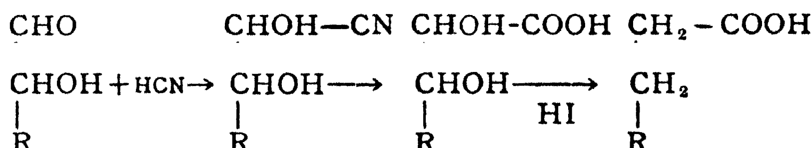
mination of the mode of linking of (i) the carbon atoms and (ii) the oxygen atoms. The type reactions for the possible functional groupings of these atoms are then utilised to detect the presence or absence of such functional groupings. Thus we have:

(A) NATURE OF OXYGEN ATOM; OXYGEN MAY BE PRESENT AS OH AND/OR CO GROUPS.

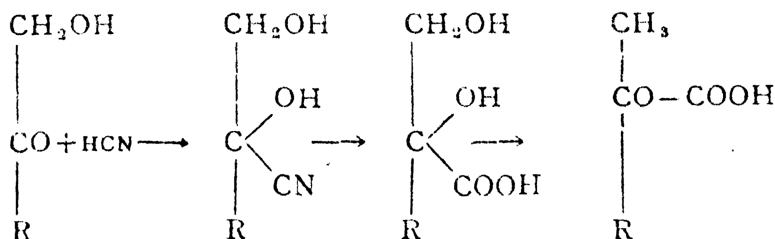
(i) *OH* groups are detected by the formation of a crystalline acyl derivative by acetylation or benzoylation. The acetyl derivatives are obtained by the action of (*a*) acetic anhydride in the presence of sodium acetate or anhydrous $ZnCl_2$, or a few drops of con. H_2SO_4 or dry pyridine or (*b*) acetyl chloride. The benzoylation is effected by the action of benzoyl chloride in the presence of sodium hydroxide or pyridine; the exact number of hydroxyl groups is determined by one of the standard methods. The presence of hydroxyl group is also indicated by methylation; one of the following methods is employed (*a*) dimethyl sulphate and alkali, (*b*) methyl iodide and silver oxide in methyl alcohol.

(ii) *CO* group: this group may be present as aldehydic *CHO* or ketonic. The usual carbonyl reagents, hydroxylamine, phenyl-hydrazine, semi-carbazide have been extensively used for the detection and estimation of the *CO* group. In the case of sugars the use of the phenyl-hydrazine in the hands of Fischer has given outstanding results. With excess of the reagent, the sugars yield the extremely useful *osazones*. (For the chemistry of osazone formation see p. 7). Further differentiation between the aldehyde and ketonic grouping is made by oxidation reactions involving the use of mild oxidising agents like bromine water, alkaline hypohalides *e. g.* NaOI or dilute nitric acid. Under these conditions, the CHO is oxidised to COOH yielding a monobasic acid containing the same number of carbon atoms while a ketone is not affected. Reaction with hydrocyanic acid, Kiliani's reaction and subsequent hydrolysis and reduction have also given important results which help to distinguish between aldehydic and ketonic compounds:

(A)

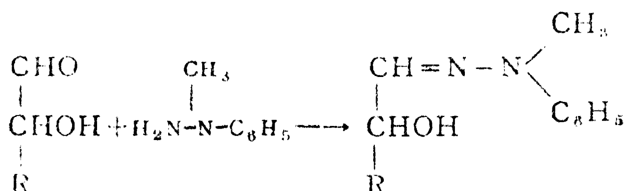


(B)

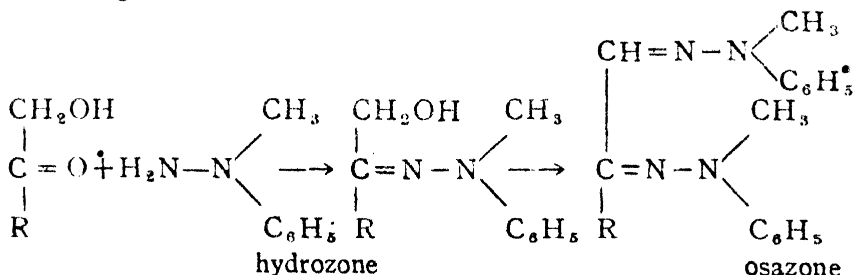


The position of the freshly introduced COOH group helps to differentiate between A and B. A is an aldehydic compound while B is ketonic.

Ketoses when heated with resorcinol and HCl (12%) give a red colouration (temporary). Also, methylphenylhydrazine $C_6H_5N{\cdot}CH_3NH_2$ can be satisfactorily used to distinguish between aldoses and ketoses. With aldoses, the colourless hydrazones are formed, the osazone formation being completely absent.



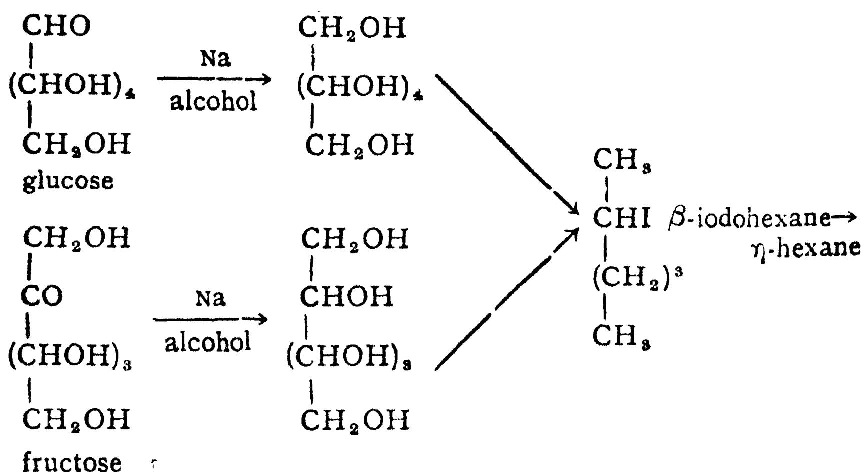
Probably the *CHOH* group resists oxidation under these conditions, and no osazone is formed. With ketones on the other hand, the yellow osazone is quantitatively formed.



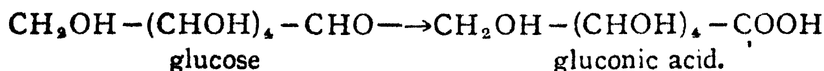
(B) Nature of the Carbon Framework. Here there are only a few possibilities. The carbon atoms may form (i) an open chain system and (ii) a closed chain system. The open chain system may be (*a*) unbranched chain system, (*b*) a branched or forked chain. The mode of determination of the nature of the carbon system is to

convert the sugar by suitable reactions which can be controlled, into simple compounds of *known* and *proved* structure. Some of the suitable reactions used are : —

(i) REDUCTION :—with sodium amalgam and alcohol. The sugar is converted into a hexahydric alcohol. The polyhydric alcohol is then reduced with concentrated hydriodic acid (in the presence of red phosphorus), when a *normal secondary-hexyl* iodide is formed. Prolonged heating however gives a normal paraffin. This indicates that the carbon atoms in the sugar molecule form a straight normal chain.



(ii) OXIDATION :—(*a*) mild oxidising agents like bromine water, hypohalogen acid (Isbell's method) and dilute nitric acid yield the corresponding monobasic hydroxy acids that can be readily identified and which contain the same number of carbon atoms.



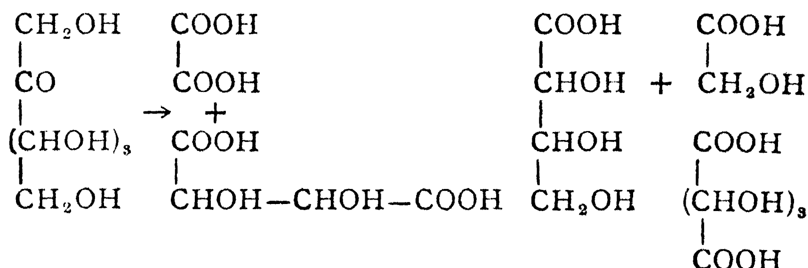
In general, aldose ——→ aldonic acid.

(*b*) vigorous oxidising agents like concentrated nitric acid and potassium permanganate oxidise the sugar molecule to a dibasic acid. The oxidation may take place in the following ways :—

(i) the two terminal carbon atoms are oxidised to COOH groups, *e.g.* glucose gives saccharic acid. This acid contains the same number of carbon atoms as the original sugar molecule and

there is no cleavage of the carbon chain. This incidentally reveals the nature of the carbon-system present.

(ii) the chain may disintegrate especially, when a ketonic CO group is present, in the middle of the chain; fructose thus gives a mixture of tartaric acid and glycollic acid or oxalic acid. The first contains a four carbon system and the second a two carbon system. The sum of the carbon atoms in the two oxidation products is equal to six *i.e.* the same as in the original sugar. The oxidation product contains also trihydroxy glutaric acid and trihydroxy-butyric acid : Such decomposition products are of immense analytical significance as they help to elucidate the constitution of the sugar *i. e.* the position of the CO group and the nature of the carbon-system present are clearly indicated.



Structure of Glucose

Of all monosaccharoses, D-glucose is the most readily available and the most important. It may be called the central compound of the carbohydrates, as the other members of the group are very closely related to it. We will now consider the evolution of the modern structural formula for this compound. There have been many important stages in the long and arduous process :—

(*i*) determination of the open chain formula, (*ii*) determination of the *spatial* or stereo-chemical formula, (*iii*) determination of the *oxide* or *lactol* or *pyranose* formula.

Liebig and Berzelius arrived at the empirical formula CO_2, as a result of the elementary analysis. A molecular formula was not possible till Tollens and Mayer in 1888 determined the molecular weight by the cryoscopic method. Their results showed that the molecular formula was $C_6H_{12}O_6$. The establishment of the structural formula resolves itself into elucidation of (*a*) the nature of the six carbon atoms and (*b*) the nature of the six oxygen atoms.

NATURE OF THE OXYGEN ATOMS :—(1) Glucose can be converted into a crystalline penta-acetyl derivative by the action of acetic anhydride and Na-acetate : $C_6H_{12}O_6 \longrightarrow C_6H_7O(OCOCH_3)_5$. This shows that it contains five hydroxyl groups, and the formula can be evolved to $C_6H_7O(OH)_5$.

(2) On mild oxidation, with bromine water, glucose gives a monobasic acid gluconic acid which contains the same number of carbon atoms : $C_6H_{12}O_6 \longrightarrow C_6H_{12}O_7$.
glucose   gluconic acid

This indicates the presence of an aldehydic (CHO) group.

(3) Glucose reacts with phenylhydrazine to form a hydrazone and then with excess of the reagent in glacial acetic acid, the insoluble *osazone* is formed.

(4) With hydrocyanic acid, a cyanohydrin, as in the case of a simple aldehyde, is formed $C_6H_{12}O_6 + HCN \rightarrow C_6H_{12}O_5OH.CN$.

Thus the presence of a CHO group is established.

NATURE OF CARBON CHAIN :—(1) Glucose on reduction with sodium amalgam and alcohol gives a hexa-hydric alcohol $C_6H_8(OH)_6$ sorbitol, which on further reduction with concentrated hydriodic acid, forms the normal secondary hexyl-iodide $CH_3—(CH_2)_3—CHI—CH_3$. Prolonged heating with HI at 100° gives n-hexane.

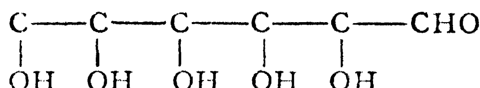
(2) The gluconic acid $C_6H_{12}O_7$ obtained from glucose by oxidation with Br_2 water, on reduction with HI and red P at 300° gives n-caproic acid.

(3) Glucose reacts with hydrocyanic acid to give a cyanohydrin which on hydrolysis gives a hydroxy acid. The latter on reduction with hydriodic acid gives n-heptoic acid (n-heptylic acid).

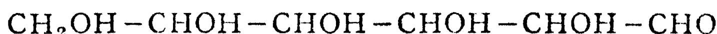
(4) Lastly, on vigorous oxidation with HNO_3 or $KMnO_4$ glucose yields saccharic acid $HOOC(CHOH)_4—COOH$ which can be reduced to adipic acid $HOOC—(CH_2)_4—COOH$ with concentrated hydriodic acid.

Therefore from (1), (2), (3) and (4), it follows that the six carbon atoms are arranged in the molecule as an open unbranched chain.

Summing up, it has been established that :—(1) the six carbon atoms from a straight chain system C – C – C – C – C – C, (ii) there are five hydroxyl groups and each one must be attached to a carbon atom (two hydroxyl groups on the same carbon atom readily eliminate water), (iii) the molecule contains one CHO group ; therefore we have :



and putting in the missing hydrogen atoms, we get the structural formula for glucose :—



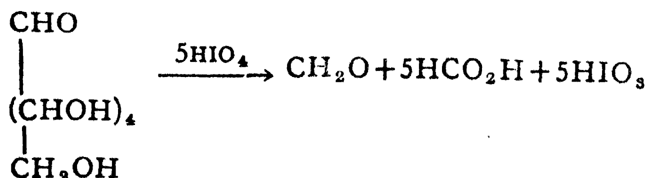
The above structure for glucose is confirmed by the Malaprade reaction. Malaprade has shown that periodic acid ($NaIO_4$ or KIO_4 and mineral acid) oxidises α-glycols in aqueous solutions and at ordinary temperatures in the absence of light and at pH 5. These conditions must be rigorously controlled, otherwise there is the tendency for over-oxidation to occur.



when R′ = H, *i.e.* when a CH_2OH group is present, CH_2O is formed. Also, with α-hydroxy aldehyde or ketone, we have



In the case of sugars, which are polyhydroxy-aldehydes or ketones, the oxidation of the molecule takes place stepwise. Glucose is thus oxidised to give one mole of formaldehyde and five moles of formic acid.



the formaldehyde is estimated as the crystalline condensation product with dimedon, and the formic acid estimated by titration.

The above results confirm the presence of one primary alcoholic group, one CHO group and four secondary alcoholic groups hence the structure assigned to glucose.

Pb-tetra-acetate in glacial acetic acid can also be used to oxidise α-glycols and hence a sugar; the oxidation proceeds similarly. However, the reagent is stereo-specific and can oxidise only *cis* α-glycols; periodic acid does not differentiate between the *cis* and the *trans* α-glycols; also the sugars are readily soluble in water which greatly facilitates the oxidation of the molecule with periodic acid. Hence periodic acid is the reagent of choice in carbohydrate chemistry.

STEREOCHEMISTRY OF SUGARS

The above structural formula for glucose contains four dissimilar asymmetric carbon atoms: $(CHOH)_4$. The number of possible stereo-isomers, according to the theory of Van't Hoff and Le Bel, would be $2^4 = 16$. As far back as 1856, simple sugars like mannose, galactose were isolated from natural sources, and they were found to be isomeric with glucose but structurally identical with it. However, the exact isomeric relationship between them presented a problem which appeared quite insoluble. There were other difficulties also. The sugars were difficult to crystallise and formed a syrup. They were also sensitive to heat and chemical reagents. But the genius of the great organic chemist E. Fischer overcame all the difficulties and successfully clarified and consolidated our knowledge of these monosaccharoses. It was a brilliant period of vigorous research extending over many years and ending with the establishment of the structure and configurational relationships of the monosaccharoses. E. Fischer worked out a series of important reactions which have proved of immense value in the attack on the molecular configuration of the monosaccharoses. Some of the fundamental reactions employed by him were:—

(*a*) osazone formation,

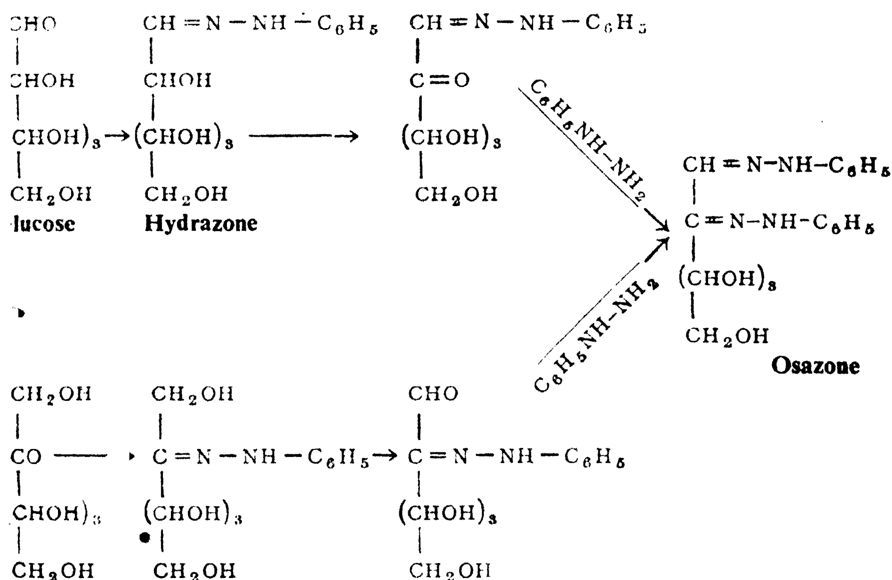
(*b*) extension of the cyanohydrin reaction (Kiliani's reaction),

(*c*) reduction to alcohols,

(*d*) oxidation to monobasic acids and to dibasic acids, and

(*e*) degradation methods:—(i) Wohl's method and (ii) Ruff's method. These reactions will be discussed in detail below —

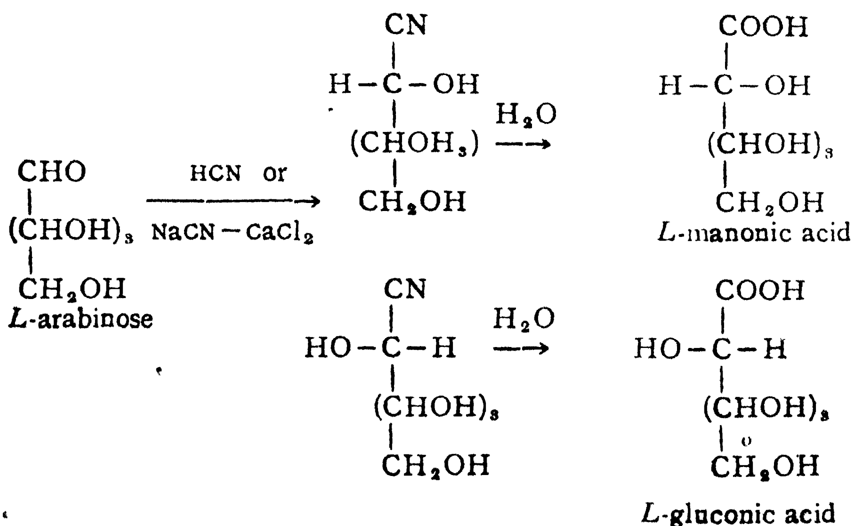
(*a*) OSAZONE FORMATION :—Fischer found that with excess of phenyl-hydrazine in acetic acid solution the simple sugars gave sparingly soluble crystalline compounds which he called 'osazones' (for chemistry see p. 7). He further found that glucose and fructose which were isomeric gave the identical osazone.



The formation of osazone thus involves the two end carbon atoms (from the aldehyde or ketone end) and changes them to the same form. The isomeric sugars, glucose and fructose whose isomerism is due to the difference in the constitution and configuration of the first two carbon atoms, are thus converted into an identical product. It follows therefore that the two sugars have the remaining parts of their molecules (the last four-carbon-system) identically constituted and spaced. This reaction has been extensively used by Fischer in elucidating the internal spatial relationships of the sugars. The sugar, mannose, isomeric with glucose yields the same phenyl-osazone and accordingly it differs from glucose in the

configuration of the carbon atom next to the aldehyde group. Sugars which are related to each other as glucose and mannose, are termed "*Epimers.*" An important property of the latter is that they are mutually interconvertible. They are structurally identical but differ only in the disposition of the H and OH groups attached to C_2.

(*b*) KILIANI'S REACTION :— The reaction of the sugar with hydrocyanic acid and subsequent hydrolysis to a monobasic acid was developed by Kiliani. He applied it to *L*-arabinose and obtained a monobasic acid, later on identified as *L*-mannonic acid. Fischer repeated the work and isolated two products (as required by theoretical considerations), *L*-mannonic acid and *L*-gluconic acid.



That the two acids thus formed are epimeric is established by the fact that on heating with quinoline at 140°C, each is partially converted into the other.

The cyanohydrin synthesis introduces a new asymmetric centre and hence the two acids formed, are **Epimers.** As the two acids are not related to each other as object and its mirror image, they are diastereoisomers. They are not necessarily formed in equal quantities because the asymmetry of the molecule exerts a spatial directive influence on the addition of HCN, Fischer further found that these

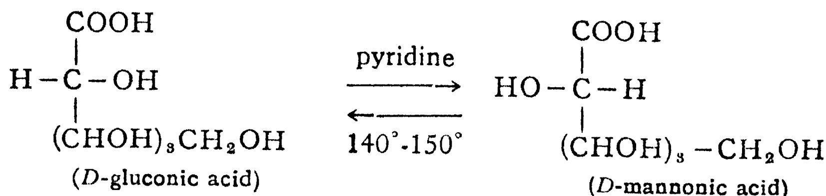
acids which existed in lactone forms could be successfully reduced with sodium amalgam in slight acid conditions to aldoses. Reduction in alkaline conditions tranforms the lactone into a polyhydric alcohol. Here was a method of synthesising a new aldose sugar containing one more carbon atom than the original sugar. Apart from the synthetic advantage, the method revealed a genetic relationship between the new aldoses obtained and the original aldose. The configurational formula of glucose is thus related to that of arabinose

The symmetry or dissymmetry of $(CHOH)_4$ system is studied by converting both the terminal groups CHO and CH_2OH, either to CH_2OH or to COOH. This is achieved either by reduction or by oxidation reactions.

(*c*) REDUCTION TO ALCOHOLS :—The sugars which are polyhydric aldehydes or ketones are reduced to polyhydric alcohols. Reduction is effected electrolytically or by Na-amalgam or by Ipatieff's method (H_2 under pressure). Catalytic reduction is preferred to chemical reduction with Na and alcohol because the latter involves structural rearrangement (*i.e.* enediol formation) and is very slow. These alcohols are either optically active or inactive thus revealing the asymmetry or symmetry of the molecules. The symmetry or asymmetry of the original sugar molicules, is then readily deduced. Galactose (isomeric with glucose) on reduction gives the optically inactive alcohol, dulcitol, whence it follows, that the disposition of the $(CHOH)_4$ system in the molecule is symmetrical. Glucose on reduction gives sorbitol which is optically active. Hence the $(CHOH)_4$ system in glucose is not symmetrical. These results account for the isomerism between galactose and glucose molecules.

(*d*) OXIDATION TO ACIDS :—(i) Aldoses on oxidation with bromine water give aldonic acids. Isbell has recently developed a very interesting electrolytic method, wherein the OBr' ion is continuously produced. The method consists in electrolysing a sugar solution containing the bromide ion ($CaBr_2$ in presence of $CaCO_3$ is used. Hydrobromic acid appears as the reduction product which in turn is being electrolysed to give the hypobromite ion. The aldose is then oxidised to aldonic acid by the hypobromite ion. Fischer found that an aldonic acid could be converted in parts, into its epimer, by

heating a solution of the acid with aqueous pyridine or quinoline. A mixture of two epimeric acids is formed.

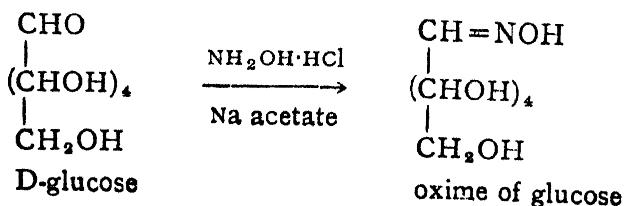


This is called epimerisation. This is a general phenomenon; when *L*-tartaric acid is heated with alkali, part of it is converted into *dl*-racemic acid and part of it into the meso acid. The two aldonic acids can then be reduced to the corresponding aldoses. The epimeric isomerism of the sugars can thus be established.

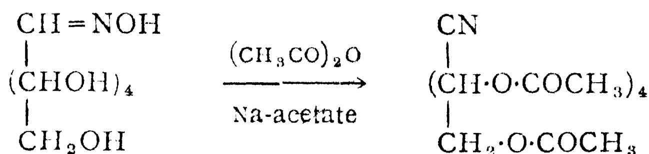
(ii) Vigorous oxidation of the aldoses with HNO_3 acid, gives dibasic acids which may be optically active or inactive. As in the case of the alcohols, the symmetry or asymmetry of the original sugars can thus be readily determined. *D*-Glucose and *L*-gulcose, which are isomeric give the same optically active dibasic acid, saccharic acid. The difference between the two sugars has disappeared on converting the two terminal groups to *COOH* groups. This indicates that the asymmetric system $(CHOH)_4$ must be the same in the two sugars.

(*e*) Degradation Methods:—A number of degradation methods have been developed. They have been used to extend and confirm the results obtained by the cyanohydrin reactions. Wohl developed a method for the degradation of the sugar molecule. The degradation takes place stepwise starting from the aldehydic end. The sugar formed by this method is of definite configuration. The various steps in the process are:

(i) Oximation of the sugar :—

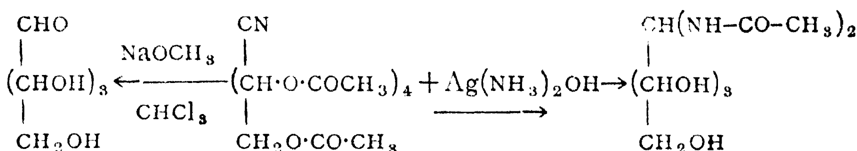


(ii) Simultaneous dehydration and acetylation of the oxime by means of acetic anhydride :—



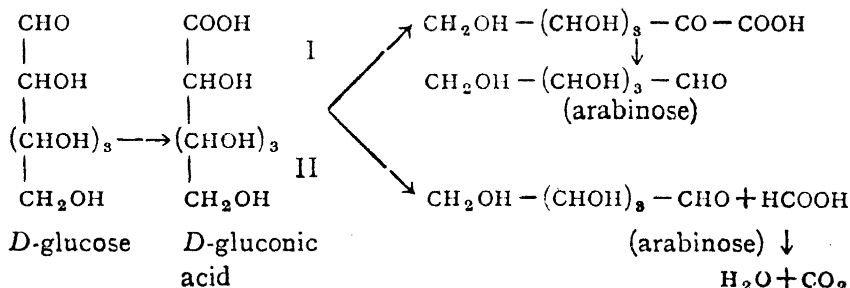
(iii) Elimination of the carbon atoms by the action of ammoniacal silver nitrate solution; the end carbon atom is eliminated and the diacetamide derivative of arabinose *i. e.* (the lower sugar) is formed. The latter on hydrolysis gives D-arabinose. (This method is applicable to most of the sugars. This method is a reversal of Kiliani's reaction as it involves the elimination of HCN). The yield is 55%.

Recently, Zemplen has shown that the yield is found to be more when $NaOCH_3$ in $CHCl_3$ is used in place of ammoniacal $AgNO_3$.



The reaction has been extended to the degradation of disaccharoses *e. g.* maltose, lactose and cellobiose.

Ruff has devised another degradation method which is much more successful from the preparative stand-point. In this method, the calcium salt of the aldonic acid is treated with hydrogen peroxide in the presence of ferric acetate (Fenton's Reagent). The probable course of the reaction is :—



The yield however is poor, because further degradation of the aldose takes place.

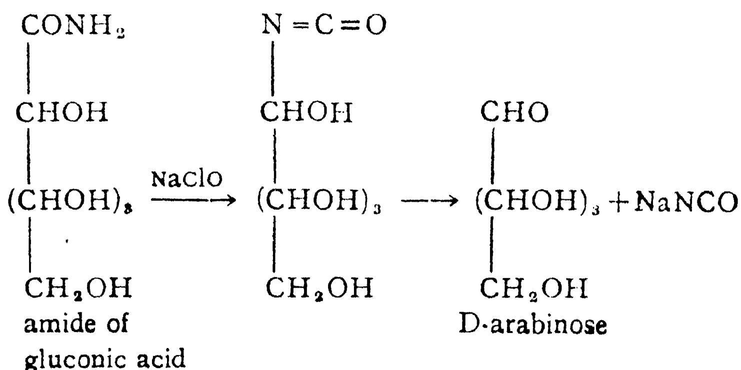
The reaction formulated under II may be compared to the behaviour of α-hydroxy-acids toward concentrated sulphuric acid or oxidising agents like potassium permanganate.



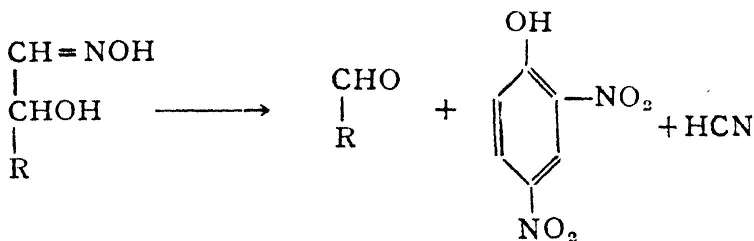
$$CH_3-CHOH-COOH \rightarrow CH_3CHO+H_2O+CO_2$$

A simpler method is to blow air or better oxygen through an alkaline solution of the aldose. The product is the lactone of the lower aldonic acid which is then converted into the lower aldose.

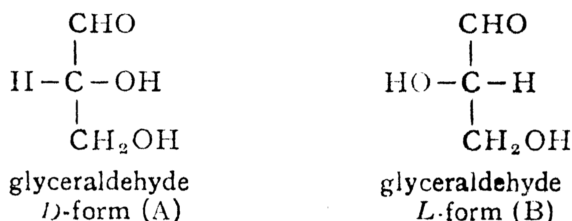
WEERMAN'S METHOD:—The principle of the method is the same as that of the Hofmann's degradation of the amides into amines. Weerman converts the lactone of the aldonic into its amide by heating it with ammonia in alcohol. The latter is then treated with alkaline hypo-chlorite ($Na_2CO_3+NaOCl$) when the lower aldose is obtained.



Recently a new method of descent in the aldose series has been announced. The oxime of the aldose is treated with 2,4*di*-nitro fluorobenzene in weakly alkaline conditions *e.g.* $NaHCO_3$ solution saturated with CO_2, when the lower aldose is formed.



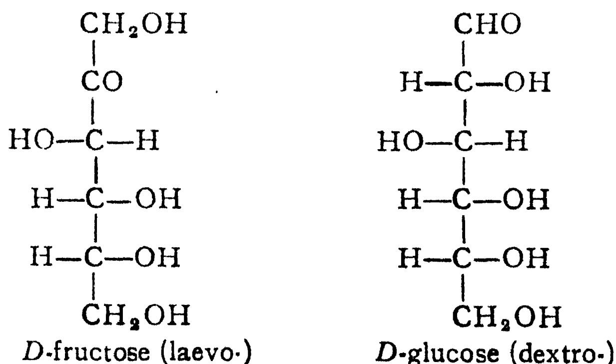
CONFIGURATIONAL TERMINOLOGY :—Configurationally the sugars have been divided by E. Fischer into two families, the *D*-family and the *L*-family. The letters *D* and *L* do not refer to the sign of the specific rotation of the sugars. The symbol *d* and *l* denote dextro rotatory and lævorotatory respectively and *dl* denotes a racemic form while *i*-refers to the *meso*-unresolvable form. Fischer used *D*-glucose as his standard compound but this led to certain ambiguities. Later, Rosanoff suggested that all the aldoses should be referred to glyceraldehyde *i.e.* glycerose (which contains one asymmetric carbon atom)—as the ultimate reference compound and he represented the *D* and *L* forms as below :—



glyceraldehyde *D*-form (A) glyceraldehyde *L*-form (B)

At first, these assignments were arbitrary but in 1951, they have been found to be correct by the Xray crystallographic studies.

Allocation of the sugars to the "*D*" and "*L*" families is made on the basis of the configuration of the bottom-most asymmetric C atom, when the compound is written with the reference group (CHO, COOH or CO) at the top. If the bottommost C atom has the configuration as in A, the sugar is said to belong to the "*D*" family; and if its spatial arrangement is as in B, the sugar is assigned the "*L*" family.

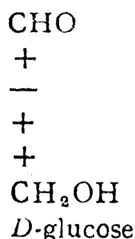


D-fructose (laevo-) *D*-glucose (dextro-)

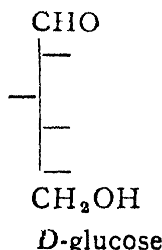
The sign of rotation of the sugar is indicated by adding the

words 'dextro' or 'laevo' as the case may be, thus *D*-(dextro) glucose, *D*-(laevo) fructose.

There is another method (due to Wohl) of writing the configurational formula of a sugar. The group *H—C—OH* is indicated by a positive sign (+), while *HO—C—H* is indicated by a negative sign (—). Glucose would then be represented as :



Rosanoff and others employ still another mode of representation. The position of the hydroxyl group is indicated by a horizontal line (—) either to the right or left of a vertical line depending on the right or left position of the OH group. Thus we have :



The letters *D* and *L* are used to represent the family relationships ; the sign of rotation is indicated by + or − ; thus we have D − fructose and L + arabinose.

CONFIGURATION OF GLUCOSE—We shall now consider the procedures by which the configuration of the glucose molecule is arrived at. Glucose contains four asymmetric carbon atoms and hence exists in 16 isomeric forms. They are :

D and L glucose	D and L galactose
D and L mannose	D and L talose
D and L gulose	D and L allose
D and L idose	D and L altrose

Of these, fourteen are known (*l*-allose and *l*-altrose are still unknown). Only twelve have been synthesised and configurations assigned to them.

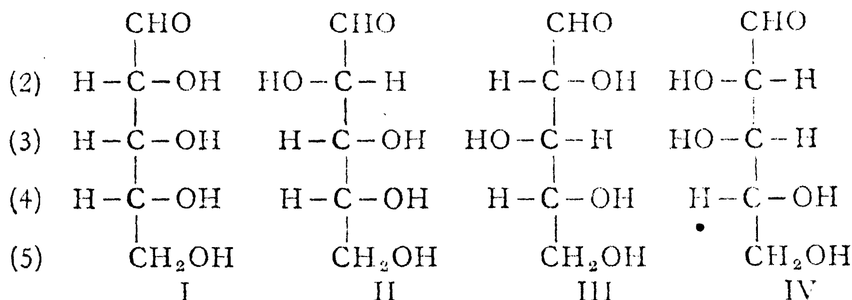
The configuration of glucose is determined by one of the following methods based on :—

(*i*) Relation to arabinose
(*ii*) Relation to saccharic acid
(*iii*) Relation to tartaric acid.

We shall discuss here only the method depending upon the relation to arabinose. In this method the configuration of arabinose is first established. Arabinose is an *aldo-pentose* $C_5H_{10}O_5$. The pentose contains three asymmetric carbon atoms and hence exists in eight ($2^3 = 8$) enantio-morphic forms which arrange themselves into four pairs (*D* and *L*) of optical isomers. They are known as :—

D and *L* arabinose
D and *L* ribose
D and *L* xylose
D and *L* lyxose.

The possible configurations for the four D forms are :

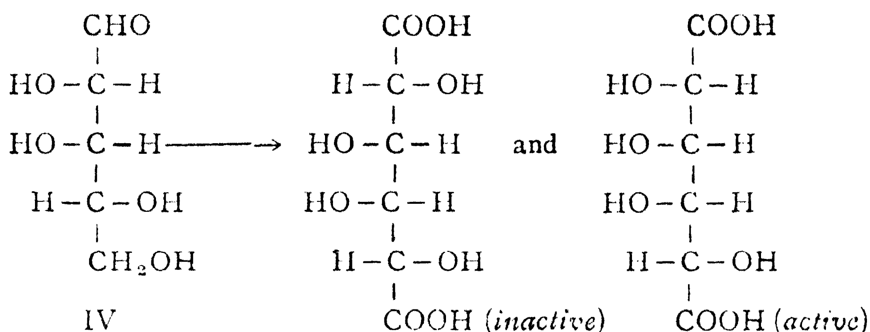


The other four are the corresponding *L*-forms. All these eight pentoses are known.

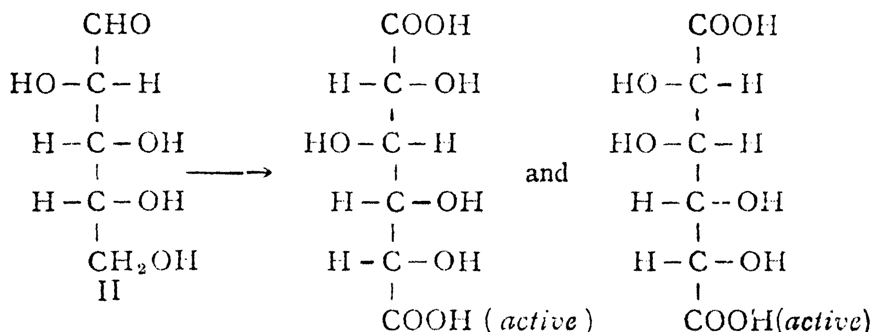
(*i*) Arabinose and ribose give the same osazone and hence they are epimeric. Therefore, the configurations of carbon atoms 3 and 4 must be the same in the two sugars. Hence if arabinose is I, ribose is II or *vice versa* ; and if arabinose is III, ribose is IV or *vice versa*.

(*ii*) Arabinose on oxidation with nitric acid gives a dibasic acid which is optically *active*, and ribose gives a dibasic acid optically *inactive*. Configurations I and III on oxidation will give optically *inactive* acids (symmetrical molecules) while II and IV will form optically *active* acids. Hence arabinose must be represented by II or IV.

(*iii*) Arabinose with hydrocyanic acid and subsequent hydrolysis gives two acids which on further oxidation give a mixture of *two optically active* dibasic acids *viz.*, saccharic and mannosaccharic. Under these conditions IV will give two acids one of which is *active* and the other *inactive*—

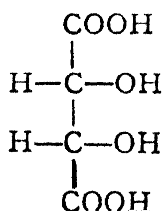


While II gives a mixture of two active dibasic acids :—



Hence arabinose must be assigned the configurational formula II. Ribose is the epimer of arabinose and has the configuration I.

The configurations to *D*-arabinose and *D*-ribose can be assigned by the following method : *D*-arabinose on degradation by the Ruff's method, gives *D* erythrose which on oxidation gives *meso*-tartaric which has the configuration :

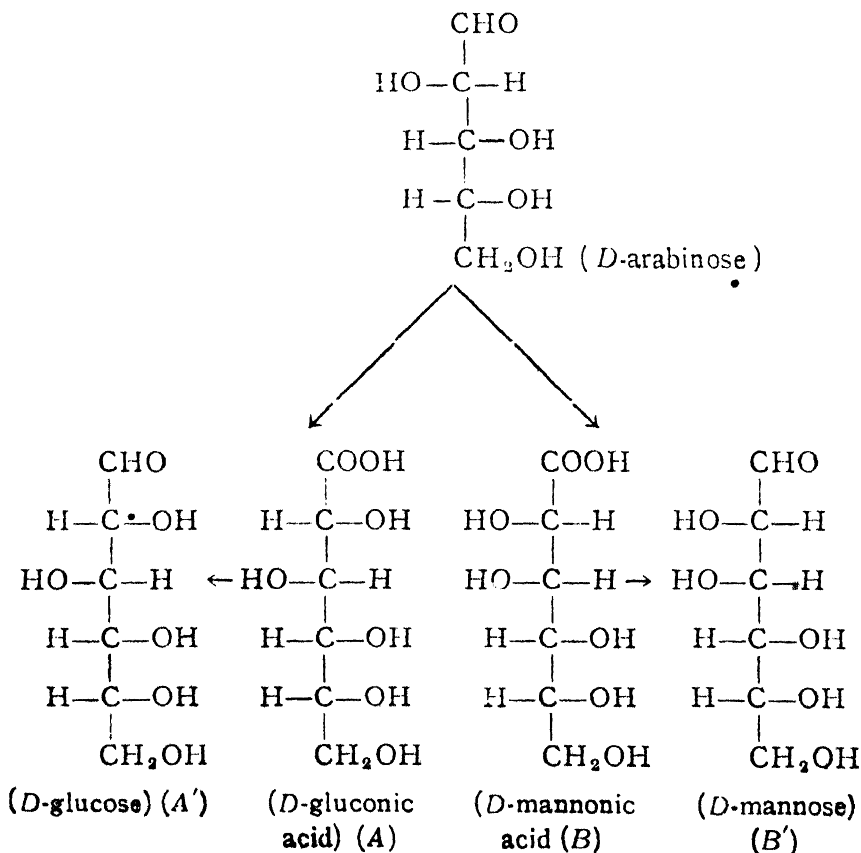


Hence arabinose must be either I or II.

But *D*-arabinose on oxidation with nitric acid gives an optically active dibasic acid therefore it must be assigned the configuration II. (The formula I contains a plane of symmetry).

Xylose on oxidation yields an *inactive* dibasic acid and hence must be represented by III. Lyxose, which is the epimer of xylose will be IV.

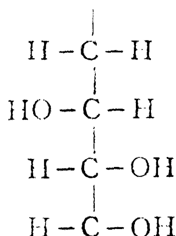
The configuration of *D*-glucose is then derived from that of arabinose, as *D*-arabinose with hydrocyanic acid and subsequent hydrolysis gives a mixture of *D*-gluconic and *D*-mannonic acid. The lactones of the acids can then be converted by reduction into the corresponding aldoses, *D*-glucose and *D*-mannose respectively.



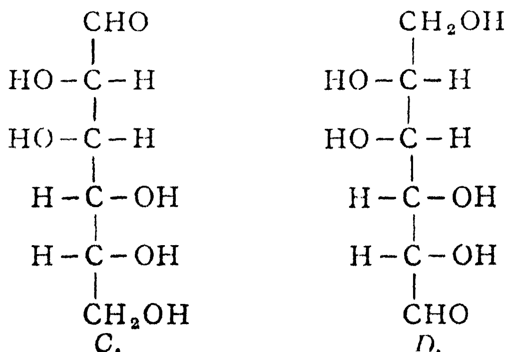
Hence *D*-gluconic acid must be either A or B. The formula B is excluded on the following groups:—

D-glucose and *L*-gulcose which are isomeric and possess the structural formula $CH_2OH-(CHOH)_4-CHO$, on oxidation give monobasic acids which are isomeric. Further oxidation of the monobasic acids results in the formation of the same dibasic acid, *D* saccharic acid. Hence it follows that the four carbon system—$(CHOH)_4$—in the two sugars is the the same. But the configuration of the system is such that when the two end *COOH* groups (in the dibasic acid) are replaced by *CHO* and CH_2OH *i.e.* dissimilar groups, two *isomeric* sugars should be possible.

Therefore *D*-glucose and *D*-gluconic acid must possess such a four carbon system that on changing the relative positions of CHO and CH_2OH groups, two isomeric sugars must be possible. This system obviously is:

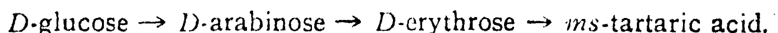


which is present in A. The system present in B is such that it gives rise to only one sugar; on transposing the terminal groups CHO and CH_2OH, we have C and D.



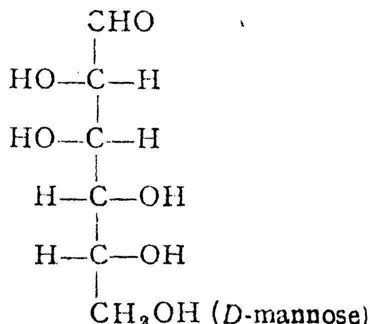
But if D is rotated through 180° in the plane of the paper (CHO group must be written at the top, in every monosaccharose formula) it becomes identical with C.

Hence *D*-glucose must be assigned the formula *A′*. The configuration of *D*-glucose may also be deduced from the following degradation reaction :

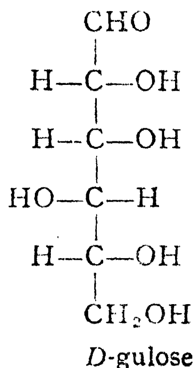


The configurations of the other hexoses are then established by considering their individual relationships to the *D*-glucose molecule.

CONFIGURATION OF *D*-MANNOSE :—*D*-mannose is the epimer of *D*-glucose (they give the same phenyl-osazone). Therefore, it has the configuration.

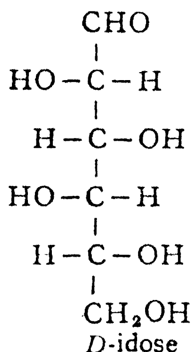


CONFIGURATION OF *D*-GULOSE :—*D*-glucose and *L*-gulose on oxidation give the same saccharic acid. Hence they must contain the same $(CHOH)_4$ system and the formula for *L*-gulose is obtained by interchanging the positions of the CHO and CH_2OH groups in the formula for *D*-glucose. The formula for *D*-gulose is then derived from that of *L*-gulose.



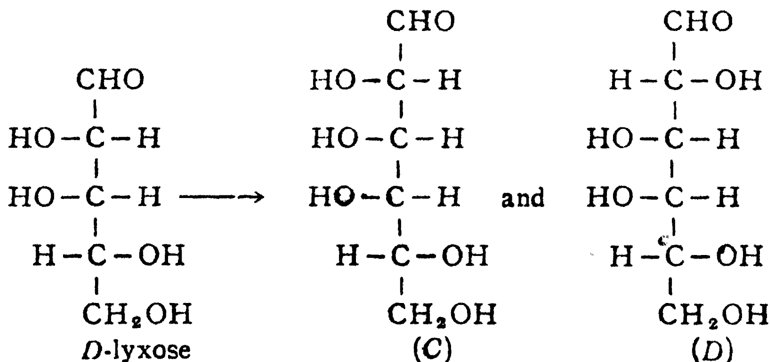
D-gulose

CONFIGURATION OF *D*-IDOSE :—*D*-idose is the epimer of *D*-gulose. Hence the configuration is :—



D-idose

CONFIGURATION OF *D*-GALACTOSE :—The configuration of this sugar is deduced from that of *D*-lyxose. The latter with hydrocyanic acid and subsequent hydrolysis and reduction of the lactone gives a mixture of two sugars which will have formulas *C* and *D*.



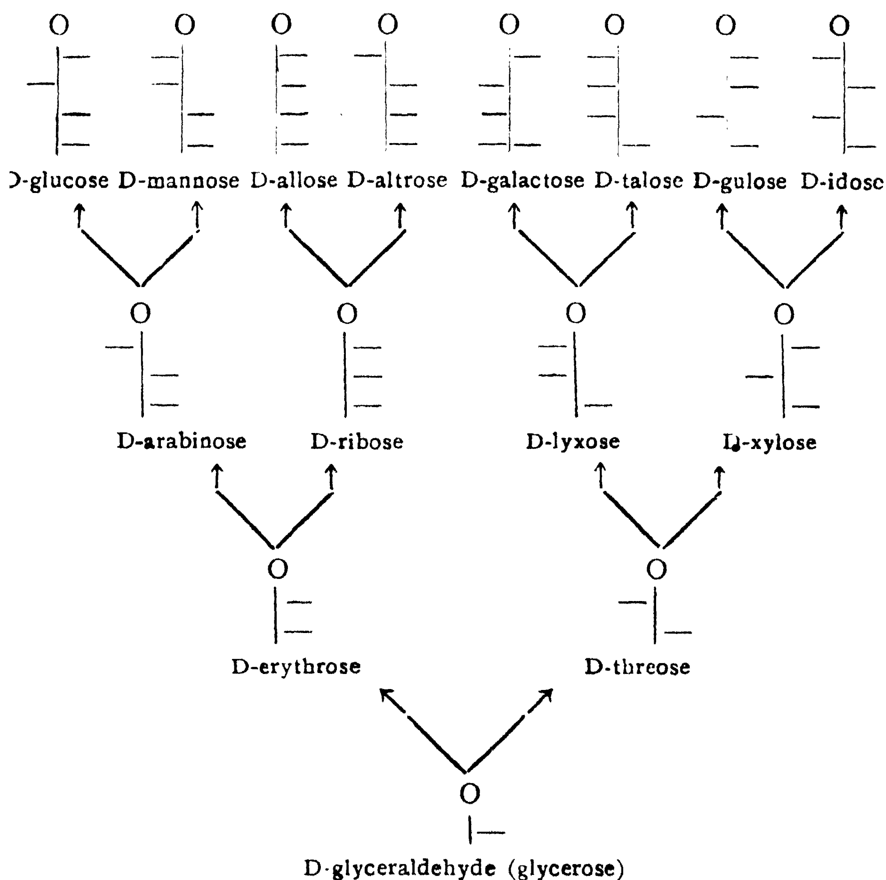
Now *D*-galactose on vigorous oxidation gives a dibasic acid, mucic acid, which is optically inactive. Therefore, it must be represented by *D*, *C* gives a dibasic acid which is optically active.

CONFIGURATION OF *D*–TALOSE :—*D*–Talose and *D*-galactose give the same osazone. Hence talose must be represented by *C*, the epimer of D.

Thus, the configurations of all the pentoses and the following hexoses have been established. The hexoses whose configuration have been established are :—

D and *L* glucose
D and *L* mannose
D and *L* gulose
D and *L* galactose
D and *L* talose
D and *L* idose

ROSANOFF'S CLASSIFICATION :—According to Rosanoff all the aldoses can be looked upon as being derived from *D*-glyceraldehyde by successive cyanohydrin reactions. The elaboration of the *D*-series of aldoses according to him is follows :—(The position of the OH group is indicated by a horizontal line and the CHO group is represented by a circle).



This classification is independent of the actual establishment of these relationship by experiment. Wohl has been partly successful to achieve some of these conversions.

Structure of Fructose

D-Fructose is the most common ketose; it is found together with *D*-glucose in honey, cane-sugar and the sweet juices of fruits. Commercially, it is obtained by the hydrolysis of inulin, a kind of starch obtained from dahlia tubers and jerusalem artichokes. Inulin is a stored food; it is a white powder readily soluble in water and insoluble in alcohol. It is *l*-rotatory. It possesses no reducing properties and gives no colour reaction with iodine. It is resistant to the action of alkali. Probably, the inulin molecule is built up mainly of γ-fructose units; a few glucose units are found to be present as terminal as well as constituent units of the chain.

CONSTITUTION OF *D*-FRUCTOSE:—The structural formula for *D*-fructose is based on the following evidence:

(*i*) Fructose has the molecular composition $C_6H_{12}O_6$.

(*ii*) With acetic anhydride and sodium acetate, a penta acetyl derivative is formed. Hence five hydroxyl groups are present.

(*iii*) Phenylhydrazine, hydroxylamine and semi-carbazide react with it to form hydrazone, oxime and semi-carbazone respectively. These results indicate the presence of a carbonyl group. It is however not affected by bromine water or by NaOI. Hence aldehydic group is absent.

(*iv*) On reduction, with Na and alcohol, a mixture of two isomeric hexahydric alcohols is obtained. The presence of $C = O$ (ketonic group) is confirmed.

(*v*) With dilute nitric acid, glycollic acid $CH_2OH—COOH$, trihydroxy-butyric acid, trihydroxy–glutaric acid and tartaric acid are formed. The formation of glycollic acid and trihydroxy-butyric acid shows that the CO group is probably next to the primary alcoholic group *i. e.* next to the terminal C atom. The exact position of the CO group is indicated by Kiliani's work; the formation methyl-butyl-acetic acid shows that the group is next to one of the terminal carbon atoms.

(*vi*) On vigorous oxidation, fructose gives a mixture of tartaric acid and oxalic acid (glucose gives saccharic acid containing *six* carbon atoms).

(*vii*) With methyl-phenyl hydrazine, a yellow crystalline fructosazone (methyl) is obtained. (Glucose gives with this reagent only a hydrazone).

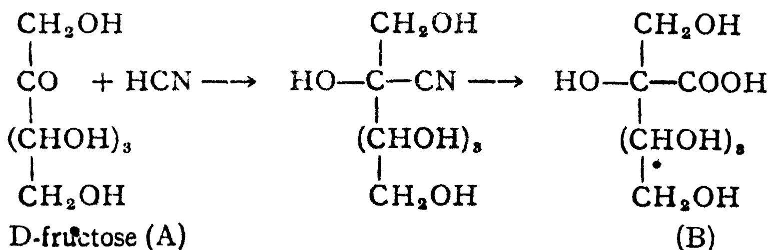
(*viii*) The alcohol C_6H_8 $(OH)_6$ obtained on reduction with sodium-amalgam and alcohol, gives normal-*sec*-hexyl-iodide on further reduction with concentrated hydriodic acid. Prolonged reaction however gives *n*-hexane. Hence the carbon atoms are arranged as unbranched chain in the molecule.

Hence from (*i*) to (*viii*) it follows that *D*-fructose is best represented by :

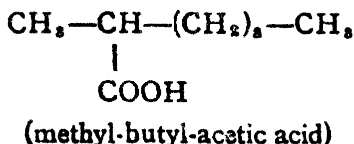


$$CH_2OH-(CHOH)_3-CO{\cdot}CH_2OH$$

CONFIRMATION—The above structure was confirmed by Kiliani. With hydrocyanic acid and subsequent hydrolysis, D-fructose (A) would give a poly-hydroxy acid (B).

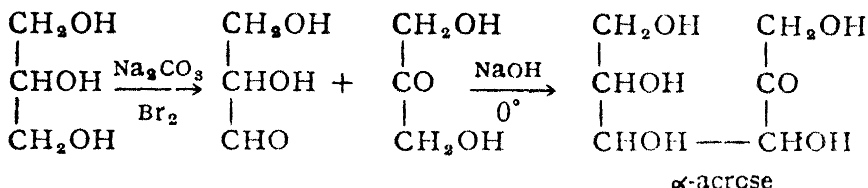


which on reduction with concentrated hydriodic acid would give.

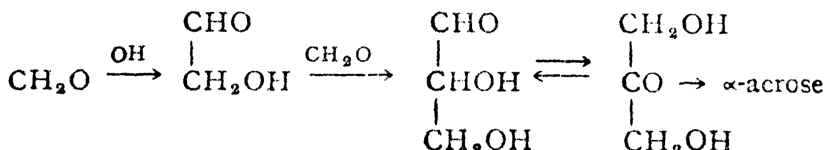


which is in perfect agreement with experimental results. (Glucose under exactly similar conditions gives *n*-heptylic acid.)

Two syntheses of fructose have been reported. Fischer developed a synthesis starting from glycerol. The important steps involved are:



In another synthesis, CH_2O constitutes the starting point.



The identity of α-acrose with *dl*-fructose was established as follows :—

(1) On reduction with *Na*-amalgam and alcohol, α-acrose gives α-acritol identical with *dl*-mannitol.

(2) *a*-Acrose is optically inactive and on fermentation with yeast gives *L*-fructose.

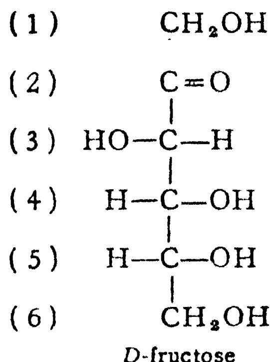
Configuration of Ketoses :—The configuration of the ketoses has been determined by a study of :—

(*a*) the osazones formed and

(*b*) the nature of the reduction products. The reduction gives a mixture of two isomeric alcohols. The conversion of *CO*-group into *CHOH*, introduces a new asymmetric centre. (Under these conditions, aldoses give only one alcohol). The same alcohols are obtained by reduction of suitable aldoses and hence their configurations can be deduced.

The configuration of *D*-fructose is derived from that of *D* glucose. The structural formula for *D*-fructose is $CH_2OH—CO—(CHOH)_3$ $—CH_2OH$ and *D*-fructose and *D*-glucose give the same osazone.

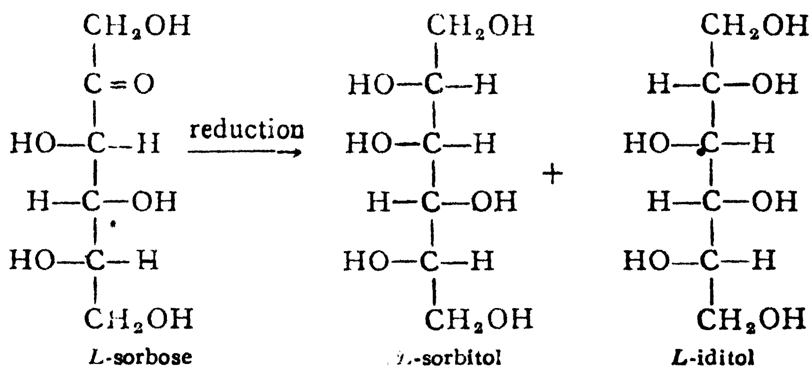
Hence the configuration of the last four carbon system must be the same in both. Hence *D*-fructose has the configuration.



D-fructose

This is further confirmed by the study of the reduction products *D*-Fructose gives a mixture of two hexahydric alcohols: *D*-sorbitol and *D*-mannitol whose configurations can be deduced from that of *D*-glucose and *D*-mannose respectively.

CONFIGURATION OF *L* SORBOSE :—This sugar gives the same osazone as *L*–glucose and *L*-idose. The configuration is further confirmed by the results of reduction.



L-sorbose *L*-sorbitol *L*-iditol

L-Sorbose is a rystaline compound m.p. 154°. It is now obtained in large quantities from *D*-sorbitol by the action of the organism Bacterium Xylinium or preferably by the action of Aceto bacter suboxydans. It is employed in the manufacture of vitamin C.

CONFIGURATION AND ENZYME ACTIVITY :—Enzymes display great selective action towards the sugars. Thus zymase contained in yeast decomposes the natural products *D*-gluose, *D*-mannose and *D*-galactose mainly into alcohol and carbon dioxide (alcoholic fermentation).

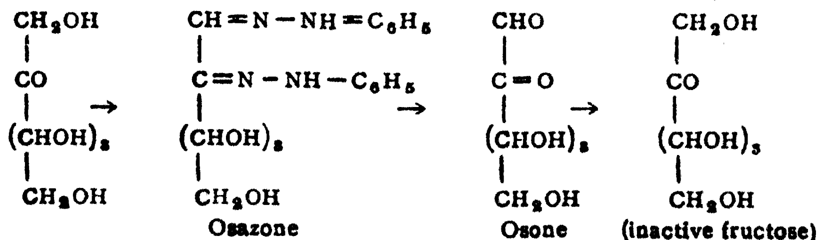


$$C_6H_{12}O_6 \longrightarrow 2C_2H_5OH + 2CO_2$$

(This reaction is the basis of the production of ethyl alcohol on a large scale). Of the ketoses, only *D*-fructose is attacked. The other isomeric hexoses or the pentoses are not similarly fermented. Fischer has shown that only those sugars which contain three carbon atoms or a multiple of three are attacked by the enzyme. Further, there is a great difference in the rate of decomposition of the sugars that are attacked. *D*-Glucose is decomposed faster than *L*-glucose and *D*-Galactose is attacked even more slowly, while the isomeric *D*-glu-cose and *D*-talose cannot be fermented at all. A comparison of the configurationl formulæ of these sugars will reveal that a slight alteration in the configuration completely inhibits the enzymic activity. Thus, there appears to be a close relationship between the configuration of the molecule and that of the enzyme that attacks it. Fischer has suggested that this relationship corresponds to that of a lock and a key. Armstrong has compared the relationship to the one existing between a hand and its glove.

SYNTHESES OF MONO-SACCHAROSES

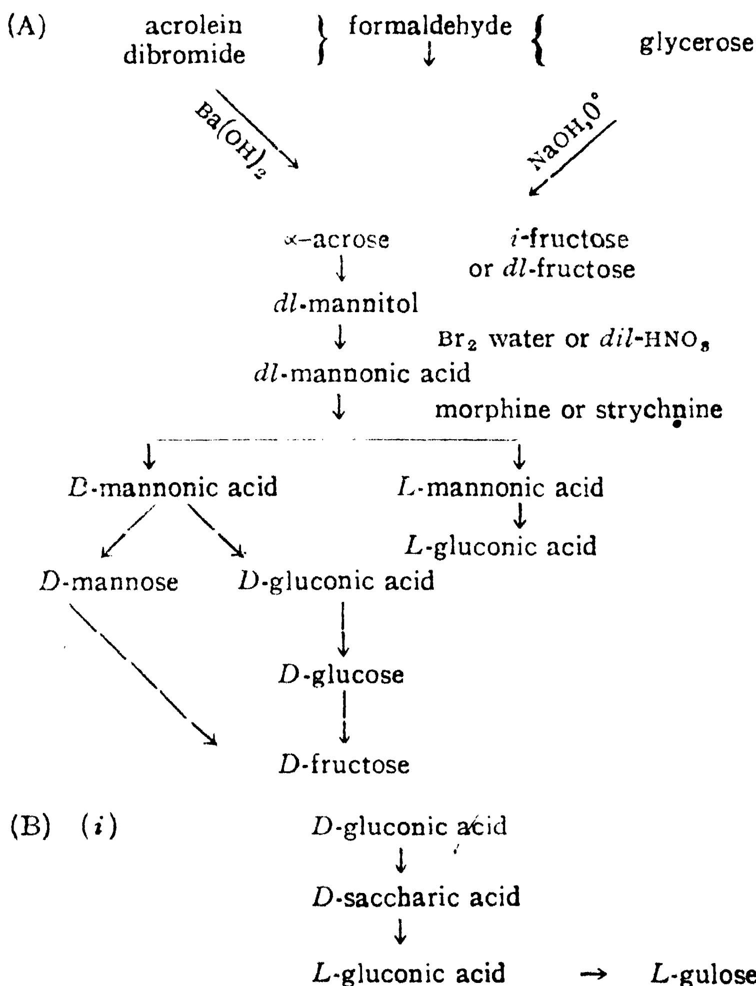
The empirical composition of the mono-saccharoses is expressed by the formula $(CH_2)n$. Such a formula suggests that these compounds might be obtained by a simple process of polymerisation of a compound with the composition CH_2O. Such a compound is known and it is formaldehyde. Many successful attempts have been made by chemists to polymerise formaldehyde under the infiuence of alkali. Fischer and Tafel obtained a sugar by the action of barium hydroxide on acrolein-dibromide. A still better method developed by them, was the use of barium hydroxide or NaOH as the condensing agent on glycerose. The product α-acrose (see p.34), was treated with excess of phenylhydrazine in acetic acid solution, when the osazone of α-acrose was formed. On acid hydrolysis, it was converted into the *osone*. The latter on reduction with sodium amalgam gave a *ketose* identical with inactive fructose—

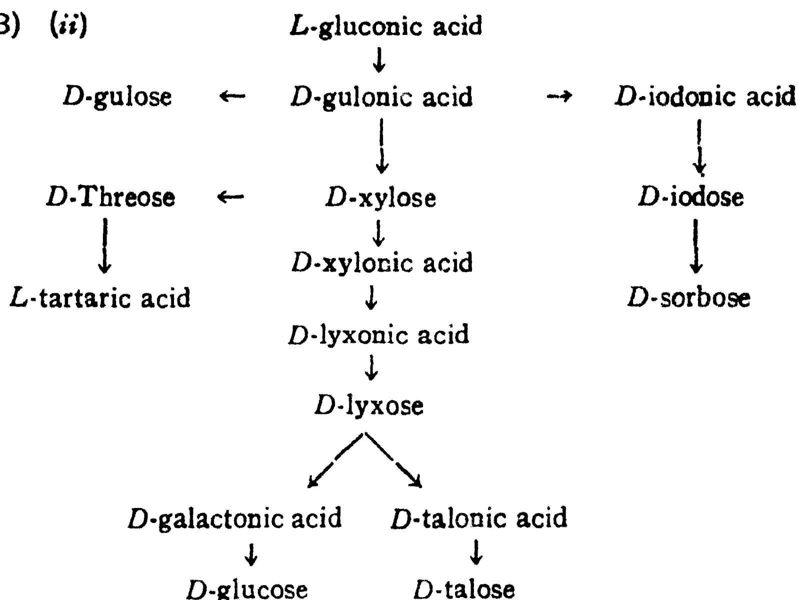


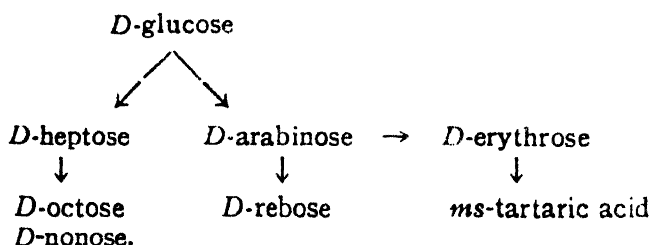
This was the first crystalline synthetic sugar. (Another isomeric sugar β-acrose was also isolated by Fischer from the syrup. One kilogram of glycerine gave 0·2 gm. of α-acrose),

Then starting from α-acrose, by skilful manipulation of many of the experimental methods, Fischer and others could synthesise the pentoses, the hexoses, the heptoses, the nonoses, etc. The other names connected with these researches are those of Tafel, Kiliani, Wohl, Ruff and Fenton.

The various stages involved in the synthetical processes can be summarised as :—







Thus starting from formaldehyde, all the hexoses, the pentoses, the higher and the lower aldoses have been synthesised.

The details of method employed including the chemistry, are as follows :

(*i*) REDUCTION.—With sodium amalgam and water, ∝-acrose was converted into *i acritol* identical with *i*-mannitol.

(*ii*) OXIDATION.—The inactive alcohol is converted into a mixture of two monobasic acids. The step is quite necessary to effect resolution of the inactive sugar into active modifications. The resolution is accomplished by the 'chemical method'. Such a method cannot be applied readily to alcohols. *i*-Mannitol is thus converted into a racemic mixture of *D* and *L* mannonic acids.

(*iii*) RESOLUTION OF THE INACTIVE ACIDS :—The resolution of inactive acids is effected by the classical methods of Pasteur

for the separation of stereo-isomers, depending upon the difference in crystal structures, the neutralisation with an optically active base, or the use of enzymes with the selective action.

(*a*) MECHANICAL METHOD.—Mechanical separation of the crystals of the alkali double salts *e.g.* Na, NH_4 or Zn, NH_4 salts.

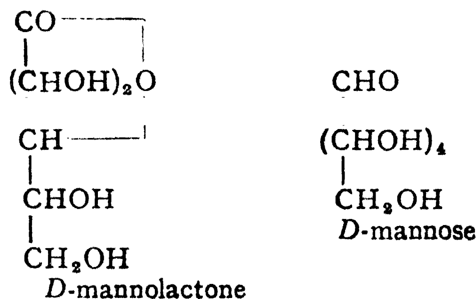
(*b*) CHEMICAL METHOD.—This involves the use of an optically active compound. A racemic mixture of acids is separated by the action of *l*-brucine or *l*-quinine, while the inactive bases are made to combine with *d*-tartaric acid.

(*c*) BIOCHEMICAL METHOD.—This method employs selective bacteria.

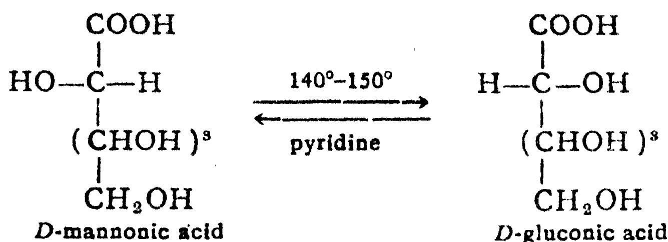
By the application of one of the above methods *i*-mannonic acid can be resolved into its optical antipodes.

(*iv*) REDUCTION OF THE LACTONE OF THE ACID INTO THE CORRESPONDING ALDOSE.—The monobasic acid, obtained from the alcohols are converted into the corresponding lactones by heating them with acids or by evaporating their aqueous solutions. The free acid or the sodium salt resists the action of the reducing agent, but the lactone which in an inner ester, is readily reduced. The lactones are crystalline compounds.

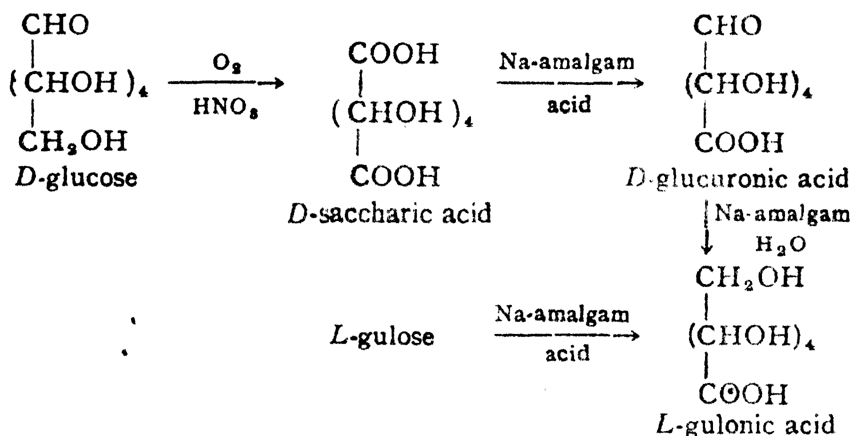
The reduction is effected by means of sodium-amalgam in the presence of a trace of sulphuric acid. This is to prevent the hydrolysis of the lactone by the formation of the sodium salt which resists reduction.



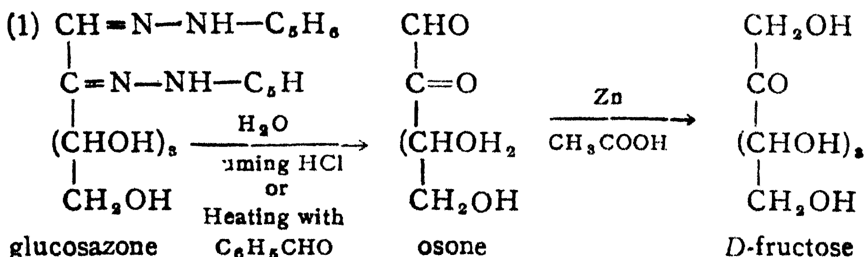
(*v*) EPIMERISATION OR INTER-CONVERSION OF ALDOSES :— This is a reaction discovered by Fischer and is of great synthetic significance. The aldonic acid is heated with aqueous pyridine or quinoline when a part of it is changed into its epimer.



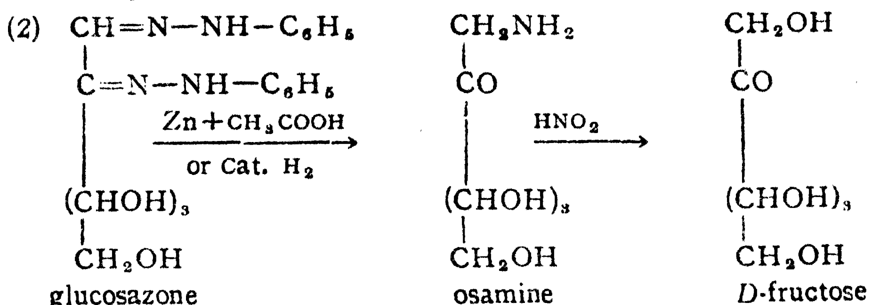
The asymmetric carbon atom (α) to the COOH group suffers inversion, *D*-Gluconic acid can then be converted into *D*-glucose by the method (*iv*) mentioned above. There is another method for the conversion of aldose into aldose. It is of limited application only. It involves the *graded* reduction of the dibasic acid obtained from the aldose into an aldehydic acid which on subsequent reduction gives the monobasic acid of a new aldose. The aldose is then obtained from the lactone by the method (*iv*) above.



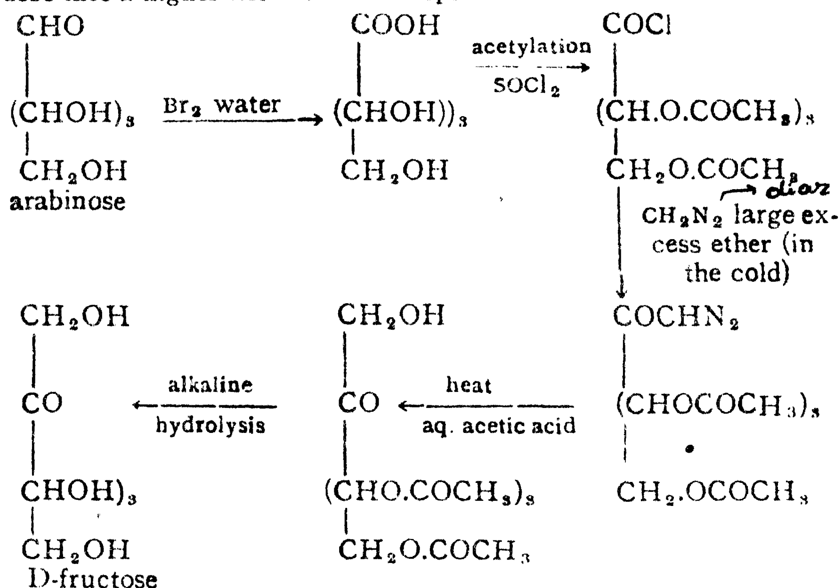
(vi) CONVERSION OF AN ALDOSE INTO A KETOSE :—The aldose is first converted into its osazone. The latter is then changed into a ketose by one of the following methods. Taking *D*-glucose as an example, *D*-glucose → *D*-glucosazone.



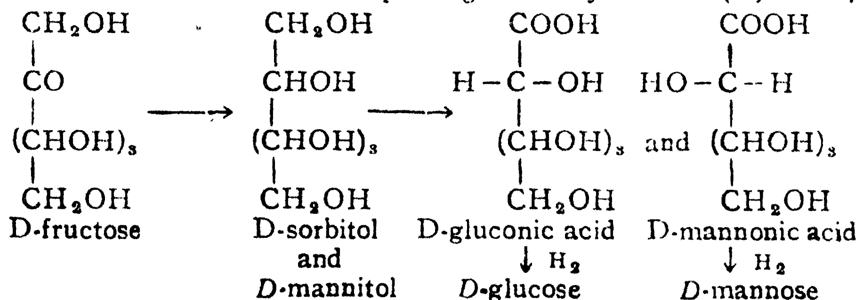
(The osone is usually isolated in the form of its lead compound)



Recently, Wolfrom has developed a method for converting an aldose into a higher ketose. The steps involved are :—



(*vii*) CONVERSION OF A KETOSE INTO AN ALDOSE.—The ketose is first reduced to the corresponding polyhydric alcohol which is then oxidised to the mixture of mono basic aldonic acids. The lactone of the acid is then reduced to a corresponding aldose by method (*iv*) above.

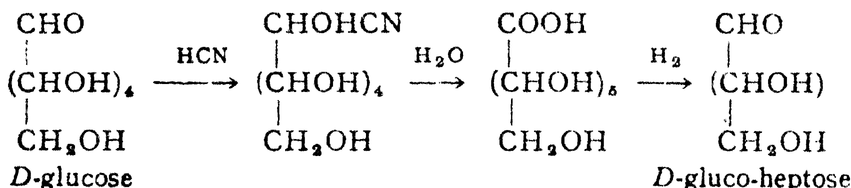


The mixture of gluconic acid and monnonic acid is converted into the sodium salts of the acids, which can then be separated on account of their difference in solubility, or the mixture of the two acids is heated with a mineral acid when mannonolactone separates out.

(*viii*) CONVERSION OF A HIGHER ALDOSE INTO A LOWER ONE—The conversion of a higher monosaccharose into a lower one (containing one atom of carbon less) is effected by a number of methods. The important ones are :—(a) Wohl's method ; (b) Ruff's method and (c) Weerman's method. The chemistry of these methods has been discussed fully, earlier.

By the application of one or all of these methods, it has been possible to break down successively *D*-glucose into *D*-erythrose and then confirm the genetical relationships arrived at by other methods.

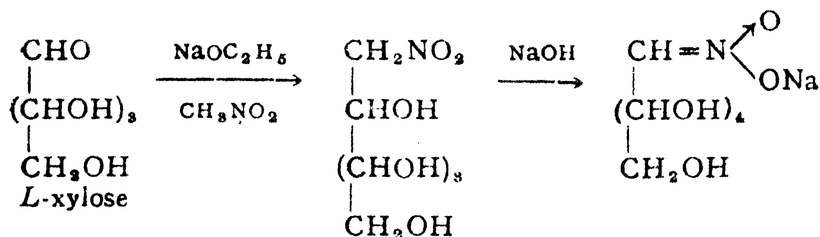
(*ix*) CONVERSION OF A LOWER ALDOSE INTO A HIGHER ONE :—*e.g.* *D*-glucose into *D*-gluco-heptose. This method was developed by Fischer and Kiliani. The aldose is converted into its cyanohydrin by the action of hydrocyanic acid. The cyanohydrin on subsequent hydrolysis gives the higher aldonic acid. The reduction of the lactone of the acid by the method (*iv*) above leads to the higher aldose.



(The source of HCN is an aqueous solution of NaCN containing $CaCl_2$).

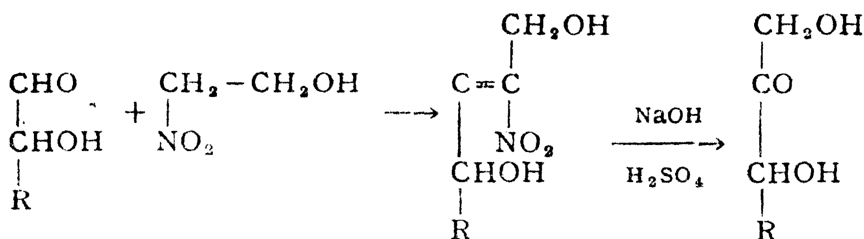
This method has been employed to obtain *D*-galactose from *D*-lyxose. Similarly new synthetic sugars up to decoses have been built up. This synthesis introduces a new asymmetric centre into the molecule and hence gives rise to a mixture of two acids (*See* p. 19). The degradation methods on the other hand give a definite stereo-chemical synthesis.

Sowden and Fischer have now developed a method of ascending the aldose series. *L*-Xylose has thus been converted into *L*-glucose, in the following way :

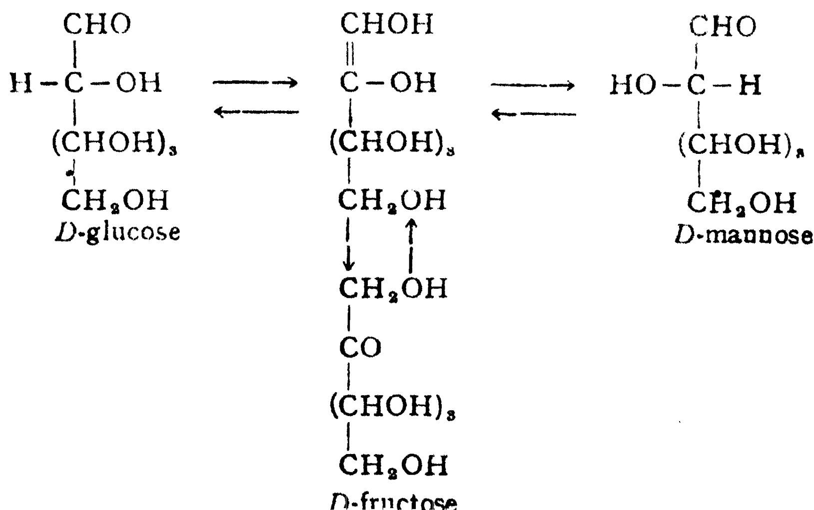


The Na salt on treatment with con. H_2SO_4 is converted into the higher aldose: CHO—$(CHOH)_4$—CH_2OH. The yield is poor, but only *L*-gulose is formed which constitutes a practical advantage.

Sowden used the same method with modifications to obtain a higher ketose.



(*x*) INTERCONVERSION OF ALDOSES AND KETOSES:—It has been observed by Lobry de Bruyn that under the influence of mild alkali like lime-water, any one of the three hexoses: glucose, mannose and fructose, is converted into an equilibrium mixture of all the three sugars. An ene-diol form is an intermediate.



The reaction further serves to indicate the close relationship existing between the three simple sugars. When an organic base like pyridine or quinoline is used in place of limewater, an aldose is converted into a ketose; *D*-xylose is thus converted into *D*-xylo-ketose.

(*xi*) CONVERSION FROM *D*-FAMILY TO L-FAMILY:—Bertrand has shown that in the presence of the sorbose bacterium, *D*-sorbitol is changed into a ketose—*L* sorbose. The sorbose bacterium is found in the juice of the berries of mountain ash. Recently, it has been discovered that Acetobacter sub-oxydans is capable of bringing about the oxidation in 3-5 days. With the original bacterium (xylinium), six weeks are required. This constitutes one of the methods of passing from '*D*' series to '*L*' series. The biological method however suffers from one limitation that it can be applied to those alcohols which have a *cis* configuration on C_2 and C_3 or C_4 and C_5. Another method for passing from '*D*' to '*L*' series, consists in racemisation of the active acid by heating it with alkali and then resolving the *dl* acid into its *d* and *l* active forms by one of the standard methods. This method, however, is limited to compounds containing two asymmetric centres like tartaric acid. The third method involves the process of graded reduction. This is exemplified by the conversion of *D*-glucose into *L*-gulose (P. 40)

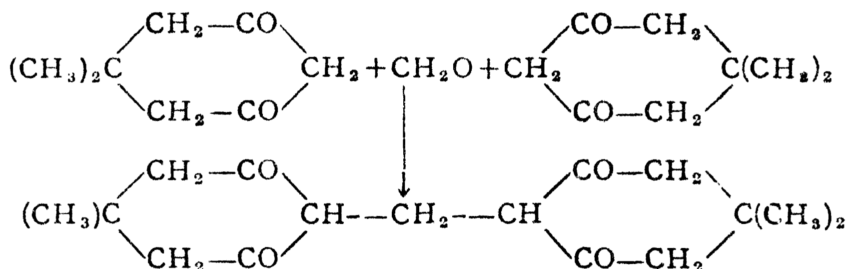
SYNTHESIS (PHOTO) OR SUGARS BY PLANTS:—In the presence of sunlight or any radiant energy, green plants are capable of synthesising simple sugars from CO_2 and H_2O. It is believed that chlorophyll, the green colouring matter of the plants plays an important role as energy carrier in this synthesis. The process is endo-thermic, energy being supplied by sunlight. According to Baeyer, the primary product of the photo-synthesis is formaldehyde.



$$CO_2 + H_2O \longrightarrow CH_2O + O_2$$

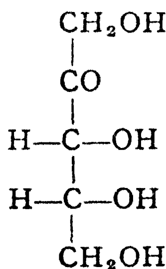
The formaldehyde is then polymerised to form glucose and more complex sugars, starches and celluloses. The reduction of CO_2 to formaldehyde has been experimentally achieved by several chemists, Fenton, Loeb, Moore and Webster under different conditions. Willstatter has also brought evidence in favour of Baeyer's hypothesis. The ratio of CO_2 assimilated by the plants to the oxygen given off is *one*, which is as required by the theory. This quotient is called the respiratory quotient. Recently G. Kleins has advanced

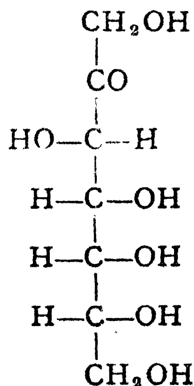
conclusive proof for the actual presence of CH_2O in plants. Dimedon is a very delicate reagent for CH_2O. Klein showed that the green leaves, on treatment with dimedon give the well-known derivative with a sharp m. p. 191. 4°C.



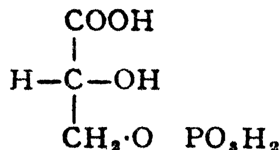
(The reagent gives the precipitate from solutions containing as little as 0. 00005 per cent of CH_2O).

It is now held that in the photosynthesis of carbohydrates ribulose and sedoheptulose play an essential part.





Ribulose diphosphate takes a molecule of CO_2 and H_2O and the product then splits into two molecules of phospho-glyceric acid.

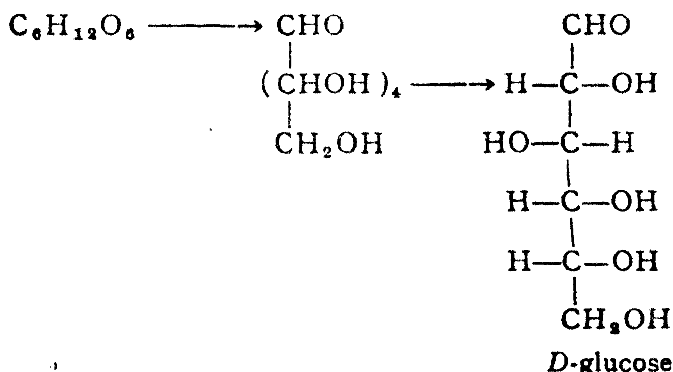


The latter is reduced to phospho glyceraldehyde two molecules of which combine to form a hexose phosphate. The hexose

phosphate may further form disacchairdes and polysaccharides. The hexose phosphate reacts with phospho-glyceraldehyde to ribulose phosphate and a tetrose phosphate. Phospho-glyceraldehyde reacts with the tetrose phosphate to form sedoheptulose phosphate. The latter then reacts with phospho-glyceraldehyde to produce ribose phosphate and ribulose phosphate; the ribose phosphate is also converted into ribulose phosphate The cycle repeats itself.

Ring or Lactol Structure for the Glucose Molecule

We have evolved for the glucose molecule an open-chain or acyclic spatial formula based on definite experimental evidence, starting from a simple molecular formula :—



D-glucose

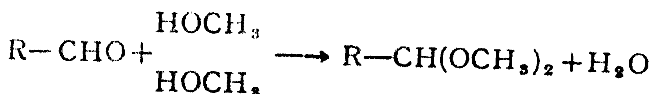
According to this formula it is a poly-hydroxy aldehyde with an *open chain structure.* However new facts regarding the behaviour of glucose have become known, which have necessitated a modification of the above structure to a *lactol (ring) formula.* These facts are :—

(i) Fuchsine Test :—Glucose does not give the usual fuchsine test for aldehydes : it does not react with $NaHSO_3$. Therefore, the absence of a free *CHO* group is indicated.

(ii) Glucose penta acetate and penta benzoate do not react with hydroxylamine to give the oximes. This indicates the absence of an aldehydic group in these esters.

(iii) There are two crystalline glucosepentaacetates. The open-chain formula admits of only one.

(*iv*) α AND β METHYL GLUCOSIDES.—Fischer obtained by heating glucose with CH_3OH and HCl gas, in a sealed tube, two isomeric glucosides with the composition $C_6H_{11}O_5OCH_3$. The α methyl glucoside melts at 165° C and has a specific rotation +157°; β isomer melts at 10° C and has the specific rotation −33°. A normal aldehyde, on the other hand reacts with dry methanol containing HCl gas to give an acetal.



$$R-CHO+\begin{matrix}HOCH_3\\HOCH_3\end{matrix} \longrightarrow R-CH(OCH_3)_2+H_2O$$

Hence glucose molecule does not contain a free −CHO group

The glucosides however, show the typical properties of a ,hemi acetal : (*a*) they do not reduce Fehling's solution. (*b*) They are very stable to alkalies but are easily attacked by acids. They do not react with HCN, and NH_2OH. They do not show muta rotation.

This suggests that C_1 carries a reactive hydroxyl group, (lactol group).

(*v*) POLY-METHYLATED DERIVATIVES.—The α and β glucosides obtained as described above on further methylation with methyl iodide and silver oxide, give a penta-methyl derivative which when hydrolysed with acids gives a tetra-methyl derivative. This differentiates one OCH_3 group *i. e.* one *OH* group from the remaining *OH* groups. The open chain formula cannot account for this observed difference in hydroxyl groups.

(*v*) MUTA-ROTATION.—It was Dubrunfant who noticed that the optical rotation of a freshly prepared aqueous solution of glucose gradually changes and falls to a constant value. The two values are + 109·6° and + 52·06°. The change is accelerated by the trace of alkali or acid. There is no decomposition because after the change, the original sugar can be recovered from the solution. Further this property is possessed by all sugars which have a reducing action (except some of the ketoses). The only possible and acceptable explanation is that D-glucose exists in two tautomeric forms in equilibrium with each other, in the aqueous solution. The open chain formula however cannot give rise to any form of isomerism.

(*vii*) STABILITY OF GLUCOSE MOLECULE—Glucose is more *stable* in air than the corresponding hexahydric alcohol. Usually the aldehyde is less stable and more volatile than the corresponding alcohol. The greater stability of the glucose molecule again suggets a *closed ring structure.*

It was on the basis of these facts that many chemists, Colley Michael, Skraup and Franchimont had suggested a *ring structure* for the derivatives of glucose. It was Tollens who first suggested that glucose molecule is not a real aldehyde but an *inner anhydride* of a heptoxycompound, similar to ethylene oxide. His suggestion was based on the analogy between the behaviour of glucose and the γ-lactones. The γ-lactones were readily formed from the correspon-ding γ-hydroxy acids and showed great stability, in agreement with Baeyer's Strain Theory. These lactones also showed muta-rotation. The suggested γ-lactol formula for glucose was :—

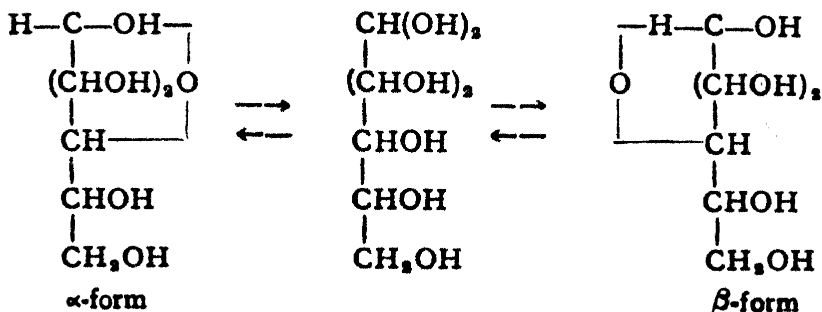
$CH_2OH—CHOH—CH—CHOH—CHOH—CHOH$



This formulation meets the objections as follows :—

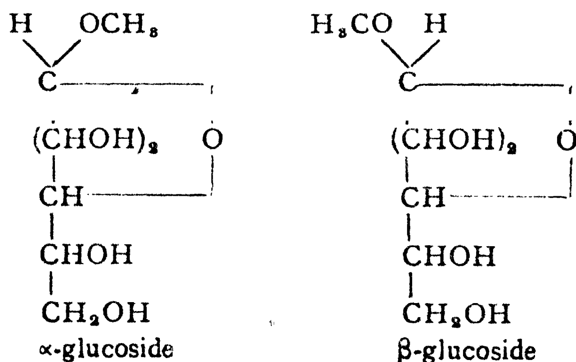
(*i*) The formula does not carry a *free* aldehydic group; on the other hand, C_1 now carries a hydroxyl group which can be readily methylated *i.e.* leads to easy glucoside formation.

(*ii*) The observed muta-rotation is now explained on the basis that there is a change in the structure of the glucose molecule during muta-rotation. The conversion thus takes place through the open chain formula, the hydrated aldehydic form (aldehydrol).



Muta-rotation is thus the reversible transformation of one isomeric form (α) into the other (β), through an unstable intermediate aldehydic form. The change occurs only in amphiprotic solvents like water or a mixture of pyridine and *p*-cresol. The change does not take place in either pure pyridine or pure *p*-cresol. It follows the course of a first order reaction. The presence of the open chain aldehydic form has been detected by reduction with the dropping Hg electrode, by Cantor. A rapid muta-rotation is associated with a higher concentration of the acyclic form.

(iii) The existence of the two isomeric methyl glucosides (α and β) can be readily explained by the closed chain formula. The cyclic formulation brings into existence a new asymmetric centre *viz.* C_1. Hence two geometric isomers are possible which correspond to the two known α and β forms.



α-glucoside β-glucoside

(iv) The ring formula also explains the hydrolysis of the pentamethyl derivative to the tetramethyl derivative which shows the reducing properties. According to the ring structure, the methoxy group on C_1 is structurally different from the other methoxy groups and hence is readily removed by hydrolysis.

(v) The stability of molecule which has been referred above, is readily accounted for on the formulation of the ring structure.

ISOLATION OF α AND β GLUCOSE :—The decisive experimental evidence in favour of a cyclic structure or oxide formula for the glucose, came with the isolation of the two glucoses by Tanret. He showed that crystallisation from cold water gave the α isomer, while the β isomer was obtained by crystallisation from water above 98°C;

crystallisation from pyridine also gave the β isomer. α-*D*-Glucose shows a rotation change of + 113°→ +52·5°, and the other β-*D*-glucose, + 19→+52·5°. They are thus mutually interconvertible The ordinary *D*-glucose represents an equilibrium mixture of these two forms in which the α form predominates. The α and β forms are sometimes referred to as "anomers". Further, Armstrong independently of Tanret and by different methods conclusively established the existence of the two isomeric α and β glucoses. Fischer had discovered that α-methyl glucoside was attacked by maltase, while the β isomer could be hydrolysed by emulsion only. Armstrong followed the enzymatic hydrolysis of the α and β glucosides polarimetrically and established the fact that the glucose liberated from the α-methyl glucoside had an initial high specific rotation and was the α isomer, while that obtained from β-methyl glucoside, was the β isomer with an initial low specific rotation.

Pyranose Structure.

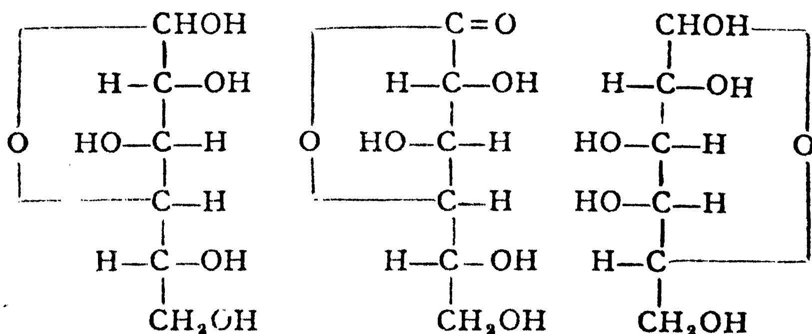
Evidence in favour of a ring structure of the glucose molecule was thus definite and conclusive. But as regards the nature of the ring, it was tacitly assumed by Fischer and others that it was a *butylene oxide* type, containing four carbon atoms and one oxygen atom. This assumption rested on a mere analogy with the γ-lactones which contained a similar ring system. No experimental evidence was led forward in support of this assumption. However, such a conclusion was sufficiently warranted by the Baeyer's Strain Theory.

In 1910, Hudson published his interesting work on the optical rotation of γ-lactones derived from the aldonic acids. He reviewed the physical properties including optical rotation of twentyfour lactones derived from sugars and was able to draw the conclusion which is now known as the "lactone rule.' The rule connects the observed sign of rotation of the lactone with the spatial configuration of the asymmetric carbon atom on which lactonisation has taken place. Thus, according to this rule, if C_4 has its hydroxyl group on the right, the lactone formed would be dextro-rctatory, but if the hydroxyl group were on the left, the sign of rotation of the lactone would be negative *i.e.* the lactone formed would be lævo-rotatory.

Hudson, later on extended it to the sugars. He argued on the basis of Van't Hoff's general principles of optical superposition and

showed that the total effect on the rotatory power of a compound is the algebraic sum of the separate effects of each of the asymmetric carbon atoms. In the case of the lactones, it is due to carbon atoms 2, 3, 4 and 5, and in the glucosidic (ring structure) sugar to 1, 2, 3, 4 and 5. Any difference between the lactones and the sugars (as ring structures) must be ascribed to the asymmetric C_1. In the case of the lactone, this carbon atom is not asymmetric, whereas in the sugar it gives rise to a mixture of two forms whose effects neutralise each other. Hence, the sign of rotation of the glucosidic sugars would be the same as in the case of corresponding lactones and would therefore depend on the right or left-handed position of the hydroxyl group involved in the glucosidic ring formation.

But these inferences of Hudson with regard to sugars were found to be at variance with the experimental evidence when the sugars were assigned a *butylene oxide ring structure* (1 : 4). Drew and Haworth suggested that the discrepancy would disappear and Hudson's rule would hold good even with the glucosidic sugars provided the sugars were represented as *amylene oxides* (1 : 5) *(six membered ring systems)*. They pointed out that the optical anomalies would be set right by such a modification of the structure. If galactose were *butylene oxide* as in (I), the ring would be on the left-hand side and the sugar should have the same sign of rotation as the lactone from the galactonic acid (II.)



(I) D-galactose **(II)** D-galactono lactone **(III)** D-galactose

However, the actual observed values are :—

D-galactose	+ 98°
D-galactono-lactone	− 78°

These values clearly indicate that Hudson's rule is not observed But a slight modification of the structure of galactose from a five to a six membered ring as in (III) removes the observed discrepancy. Thus, if galactose is represented by (III), the glucosidic ring is on the right and the sign of rotation is positive and opposite to that of the lactone, which is actually the case.

Hudson's rule when applied to the glucose series could not decide between a five and a six membered ring for glucose, because the hydroxyl groups attached to C_4 and C_5 are both on the same side and therefore the lactone would have the same sign of rotation as the sugar, either with the five membered or the six membered ring. But there were other indications that the γ-oxide structure was inadequate. They were (*i*) the isolation of four different crystalline galactose-pentacetates and penta-benzoates of glucose and (*ii*) the isolation of a third isomeric γ-methyl glucoside. These facts suggested the existence of two distinct ring systems.

Direct experimental evidence for the exact size of the ring in the glucose molecule has been adduced by Haworth and Hirst. It is based on the results of studies in oxidation of the methylated sugars. The glucose molecule contains five hydroxyl groups, any two of which may be involved in the ring formation. Further, the ring structure is very labile as is indicated by the ease with which muta-rotation occurs and the readiness with which the molecule reacts in the open aldehydic form. Under the usual experimental conditions, even by the action of mild reagents, the molecule may suffer structural alterations leading to a change in the number of atoms constituting the ring. There is every probability that the original ring structure may be ruptured and a fresh type of ring be formed in the molecule. Hence, in a study of exact nature of the ring, it is quite essential to put out action all the free hydroxyl groups in the molecule which serve as centres of formation of a fresh ring, different from the one originally present in the molecule. This 'masking' of the hydroxyl group can be done by replacing the hydrogen atom of the hydroxyl group by a suitable group. The usual procedures are acetylation, benzoylation and methylation. The acetyl and benzoyl groups, however, suffer from some limitation. They cannot survive the usual acid hydrolysis. There is also no guarantee that these groups will not migrate. On the other hand,

the methylated sugars which would contain the C—O—CH_3 group *i. e.*, an ether linkage would display great stability and resistance, towards hydrolysis which is so characteristic on an ether linkage. Further the methylated sugars possess the following useful properties from the practical stand point:—

(*i*) They crystallise very well.

(*ii*) They can be obtained readily in a characteristic form.

(*iii*) They can be purified by distillation in vacuo.

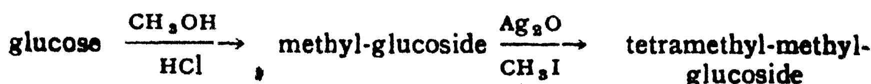
(*vi*) They are very much soluble in the common organic solvents.

(*v*) They do not suffer many migration changes.

Hence, methylation of the sugars has become a process of fundmental practical importance in the study of structural chemistry of sugars. We, now come to the experimental methods that have been evolved and perfected by pioneer experimentalists in the field. Some of the great names associated with these researches are: Purdie, Irvine, Haworth.

Methods of Methylation

1. SILVER OXIDE METHOD.—This method was developed by Purdie, Irvine and Cameron. The sugar is first converted into its methyl-glucoside, (as silver oxide will oxidise the free sugar) by Fischer's method which consists in treating a methanol solution of the sugar with an excess of dry *HCl* gas in the cold. Also, the methyl glucoside being more soluble in organic solvents than the sugar, it is better fitted for use in this method. The methyl-glucoside is then treated with methyl-iodide and silver-oxide in alcoholic solution (Methanol). Recently, dimethyl formamide has been used as a solvent and the methylation is found to be effective and efficient.



$$\text{glucose} \xrightarrow[HCl]{CH_3OH} \text{methyl-glucoside} \xrightarrow[CH_3I]{Ag_2O} \text{tetramethyl-methyl-glucoside}$$

ADVANTAGES OF THE METHOD.—The methylation proceeds under mild conditions and hence deep-seated structural alterations in the molecule are precluded. The reaction is free from the complications of racemisation, Walden inversion or other glucosidal interconversions. Hence, this method may be safely relied upon, in the

preparation of standard methylated sugar derivatives. The method can fruifully be extended to the methylation of oxidised sugar molecules.

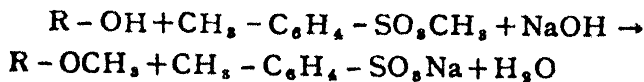
LIMITATIONS.—However, there are some limitations to this method. (*i*) The simple sugar cannot be directly used, as silver oxide has an oxidising action. (*ii*) It is applicable only to sugars for which a suitable solvent can be found. (*iii*) the reagents, methyl iodide and silver oxide, are both very expensive.

2. DIMETHYL-SULPHATE METHOD.—Denham and Woodhouse introduced a new method of methylation of cellulose, since the insolubility of the latter in organic solvents prevented the application of the silver oxide method to the problem. They employed dimethyl-sulphate in the presence of aqueous 10–30% sodium hydroxide in which cellulose is soluble to some extent, to obtain the methyl derivatives of cellulose. Haworth extended the use of the reagent to prepare the methyl derivatives of the simple sugars. However the simple sugar itself cannot be directly methylated by this reagent as the alkali is capable of causing deep-seated changes in the molecule. Usually, the methyl glycosides are first obtained which are then further methylated by this reagent ; or a very large excess of $(CH_3)_2SO_4$ is used in the initial stage, until the alkali-sensitive reducing group is methylated.

ADVANTAGES :—In this method methylation proceeds more readily and smoothly and the yields are good. (i) Methylation of the sugar proceeds in definite stages and homogeneous products representing the intermediate steps in methylation can be isolated. (ii) Mixtures of unchanged and partly methylated sugars are not formed. (iii) The final purification of the end product is simple. (iv) The reagents are very cheap. (v) It can be extended to all compounds which contain hydroxyl groups.

The only *limitation* is that the reagent is very poisonous and the operation has to be carried out under an efficient hood.

Recently the poisonous dimethyl-sulphate has been replaced by the harmless menthyl-*p*-toluene sulphonate, as a methylating agent. But it is costly.



$$R-OH+CH_3-C_6H_4-SO_3CH_3+NaOH \rightarrow$$
$$R-OCH_3+CH_3-C_6H_4-SO_3Na+H_2O$$

Another method of methylation, developed and extended by Robinson, was first used by Claisen to methylate simple hydroxy compounds. It is to treat the hydroxy-compound with methyl iodide in dry acetone (equal weight) and a good quantity of powdered anhydrous potassium carbonate or potassium hydroxide. It is applicable to a large variety of hydroxy compounds both aliphatic and aromatic.



$$R-OH+CH_3I+K_2CO_3 \rightarrow R-OCH_3+KI+KHCO_3$$

The reaction mixture is heated on a water bath or a sand bath. The yields are quite good.

3. MENZIES METHOD.—This is the thallation method. The sugar is treated with aqueous thallous hydroxide or thallous ethylate to form the thallates; the latter are then treated with CH_3I to give the methyl sugars; the reaction can be carried out in non-aqueous solvents. Thus the method is applicable where the dimethyl sulphate method fails.

4. Diazomethane is also used to methylate sugar lactones and their derivatives. The methylation is carried out in methyl alcoholic solution at low temperature.

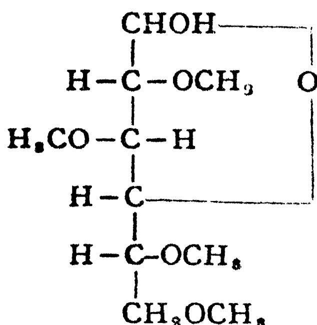
5. Recently, methylation has been effected with $NaNH_2$ in liquid ammonia and methyl iodide. The yields are satisfactory.

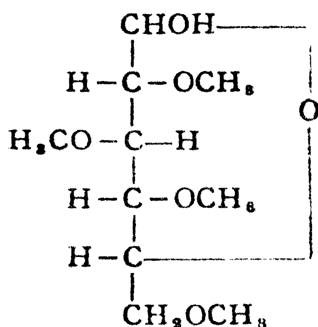
HAWORTH AND HIRST'S PROOF FOR SIX-MEMBERED RING

They started with the crystalline tetra-methyl glucose (mp 96°) obtained by the acid (5% HCl) hydrolysis of the pentamethyl glucose. The latter is obtained by methylating the α or β methyl glucoside by one of the methods of methylation described above. The tetramethyl glucose is oxidised by heating it with con. HNO^3 (D 1·42) at 90°C for three hours. The C_1 and the C atom involved in ring formation are affected. Disintegration of the molecule due to oxidation takes place which gives rise to a mixture of methylated dibasic acids containing four or five carbon atoms depending on the original size of the ring. Thus the results of oxidation can be used to ascertain the points of ring closure *i. e.* the size of the ring.

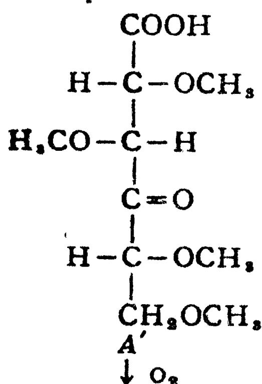
If tetra-methyl glucose, obtained from glucose has the butylene

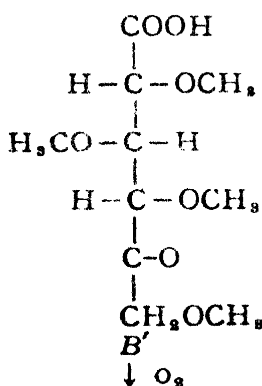
oxide or γ-oxide structure, it would be represented by A; if δ-oxide structure, then by B.

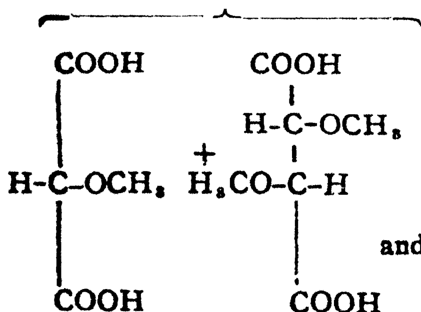




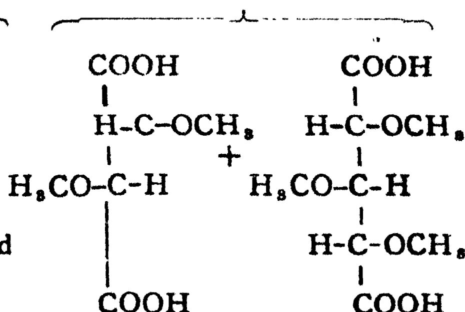
On oxidation, *A* and *B* would give *A′* and *B′* respectively which on further oxidation will give succinic or glutaric acid derivatives :—





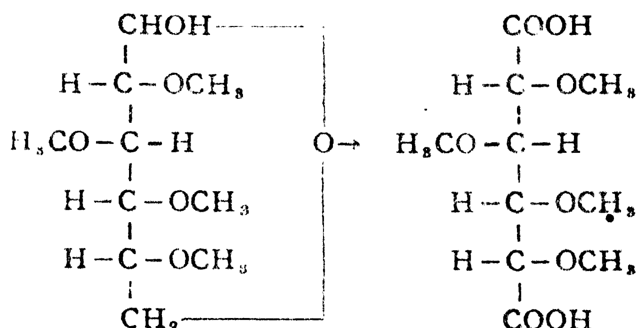


and



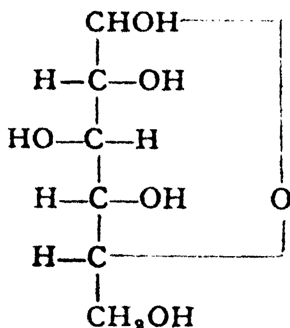
Therefore, the formation or otherwise of xylo-tri-methoxy glutaric acid is the crucial test in deciding between the two possible ring structures. Hirst identified by means of the crystalline diamides and methyl amides, *i*-xylo-tri-methoxy glutaric acid and dimethoxy succinic acid among the oxidation products of tetramethyl glucose. (Xylo indicates the configurational relationships. This acid is obtained by oxidation of 2, 3, 4 tri-methylxylose).

The formation of xylo-tri-methoxy-glutaric acid shows clearly that the methoxy groups are located on C_2, C_3 and C_4 and hence these positions could not have been involved in the ring formation in the tetramethyl glucose molecule. The ring, therefore, must be placed on C_5 or C_6. The latter possibility is then excluded as follows:—If the seven membered ring system were present in tetra-methyl glucose, on oxidation, no xylo-tri-methoxy glutaric acid would be formed, but a dibasic acid containing *six* carbon atom-system would result :—

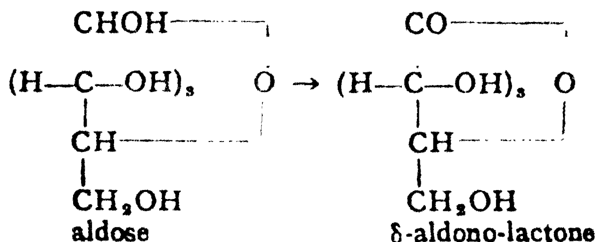


which however is not the case.

Thus, the tetra-methyl glucose obtained from α-methyl glucoside must be assinged the δ-oxide structure. This is further proved by the fact that on oxidation with bromine water, the tetramethyl glucose gives a lactone which is rapidly hydrolysed by water, a characteristic of δ lactones. Since α *D*-glucose has been definitely shown to be related to α-methyl glucoside by E. F. Armstrong, the free sugar *D*-glucose must possess the same structure (provided no ring shift takes place during the methylation). Further, as β-methyl glucoside gives the same tetra-methyl glucose, the related sugar β *D*-glucose must also have the identical oxide structure. Hence, α and β *D*-glucose possess this formula.



A still more direct proof for the ring structure for the free sugars in solution has been adduced. Hudson and Isbell have carried out interesting studies in oxidation of aldoses to aldonic acids by hypobromite ion. They have shown conclusively by polarimetric studies that during oxidation an immediate, quantitative and direct formation of the δ-lactone occurs without the free aldonic acid being formed as an intermediate product. Finally they isolated the δ-lactone by oxidising glucose with bromine water for half an hour in presence of $BaCO_3$ and extracting the product with dioxan.



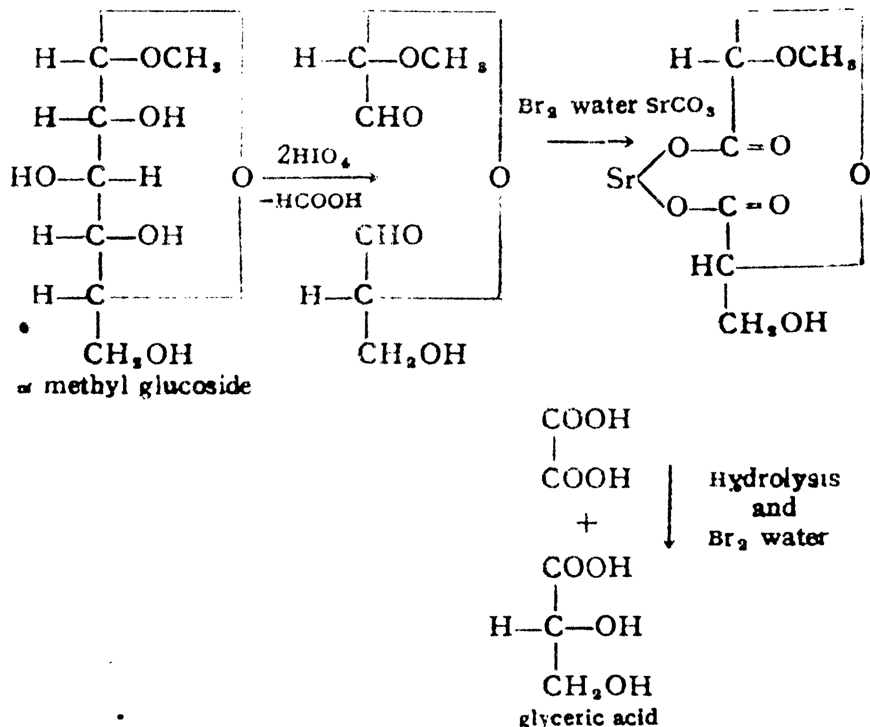
These δ-lactones are sharply differentiated from the γ-lactones. They are hydrolysed to the free acids much faster than the corresponding γ-lactones. The rate of hydrolysis of the lactones is measured by following the optical rotation as it approaches zero, on conversion to the free acid.

Lastly, X-ray measurements of free glucose molecule have shown that there is a six membered ring present in the crystalline state also.

A striking confirmation of the above six membered cyclic structure assigned to methyl glycosides, has been obtained by Jackson and Hudson. Their method involves oxidation of the methyl glycoside with periodic acid in aqueous solution. The oxygen bridge

in glycosides is sufficiently stable to resist hydrolysis during oxidation. Thus the periodate oxidation breaks open the chain of C atoms, leaving the oxide ring intact.

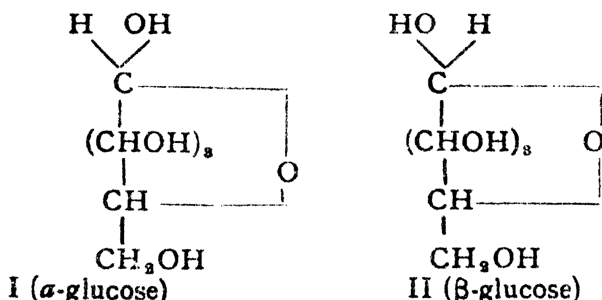
The primary product of such an oxidation is a dialdehyde. It is characterised by oxidation with Br_2 water in presence of $SrCO_3$ to form the Sr salt of the dibasic acid in crystalline condition. The free acid is then obtained by treatment with con. H_2SO_4 and its constitution established by further oxidation with Br_2 water. The various steps involved are represented schematically as follows:—



Thus with a six-membered ring, two molecules of periodic acid are consumed, with the formation of one mole of formic acid. Also, the formation of glyceric acid as the final product indioates that the secondary hydroxyl group (produced by the opening of the oxygen bridge) is in α position to the CH_2OH group. These results thus confirm the earlier assignments made by Haworth and others.

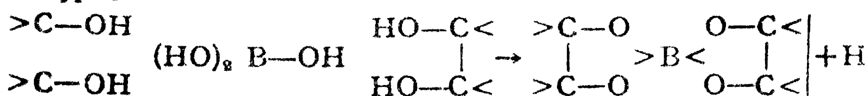
If the ring in the methyl glucoside were 1.4 or butylene oxide, periodic oxidation would not yield formic acid at all (absence of three consecutive CHOH groups).

Now, there remains the problem of the configuration of the C_1 which has become asymmetric. An empirical rule was put forward by Hudson for designating the α and β -isomers. In the D series, the isomer with the higher specific rotation is termed the α isomer and is assigned the formula (I), and the one with lower specific rotation, is the β isomer and assigned the formula (II).

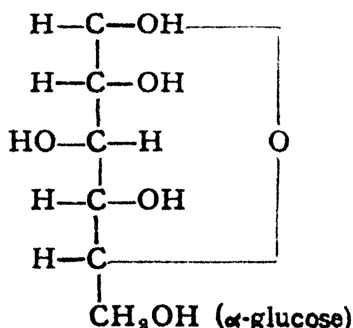


I (α-glucose) II (β-glucose)

Boeseken proposed a spatial configuration for the α and β glucoses, based on the results of electrical conductivities of the boricacid solution. He showed that polyhydric alcohols *e. g.* glycerol with two adjacent hydroxyl groups in *cis* position *i. e.* on the same side, can give co-ordinated complex compounds of the type :—



This is a strong electrolyte, which greatly increases the conductivity of boric acid solution. The conductivity of boric acid solution in the presence of α-glucose decreases, while it is increased by the presence of β glucose since, on standing, α glucose gradually changes into β isomer and *vice versa* it follows that α glucose increases the conductivity and β-glucose decreases the conductivity : hence α-glucose possesses the *cis* form.

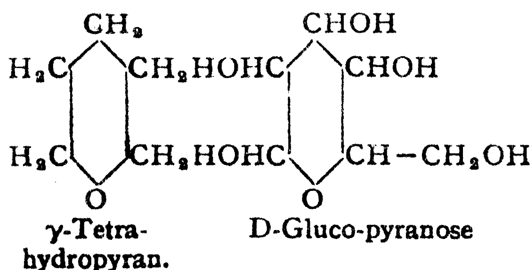


However, Boeseken's method is open to criticism because the glucosides of tetra-methyl glucose, where carbon atoms carry no *OH* groups give similar results with boric acid solution. The above configuration for α-glucose has been further confirmed by Ruber by the molecular refractivity data. The molecular refractivity for *D* light of α-glucose is 62·68°, and of β-glucose 63·70°. This is in accordance with the rule that *trans* isomer has a higher molecular refractivity than corresponding *cis* form. Recently Isbell and Pigman have proposed the following rule: when the oxygen bridge is on the right, the α-isomer is the one which is more dextro-rotating: while when the ring is on the left, the α-isomer is the one which is more laevo-rotatory. Thus, in the *D* series, the α form has the greater positive rotation while in the *L* series, the α form has the greater negative rotation.

Recently, chemical evidence in favour of the *trans* form for the β-isomer of glucose has been obtained. Glucose 1 – 2 anhydride 3, 4, 6 triacetate reacts with methanol at room temperature, in the absence of a catalyst to give β methyl-glucoside–3, 4–5 tri acetate only. It is known that when an oxide ring is opened up, there is Walden Inversion. Hence, the 1-methoxy group must be trans to C_2-OH, in the compound formed.

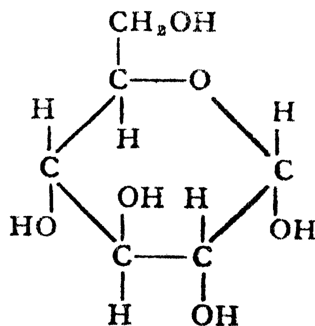
The crystallographic evidence in the case of α D-glucose, shows that the OH groups on C_1 and C_2 are *cis* to each other.*

THE HEXAGONAL FORMULATION :—Haworth has suggested that the properties of the sugars could be better explained by a hexagonal formula He showed that *D*-glucose molecule could be represented as a hydroxyl-derivative of tetrahydro-γ-pyran thus :—



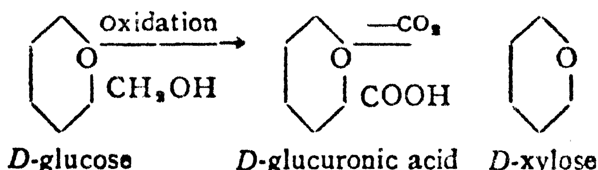
γ-Tetra-hydropyran.

D-Gluco-pyranose



This structure is also supported by X-ray spectra, (Cox). Such a formula explains readily the relation of *D*-glucose to natural

xylose which accounts for their frequent association in nature (e. g. xylan with cellulose).

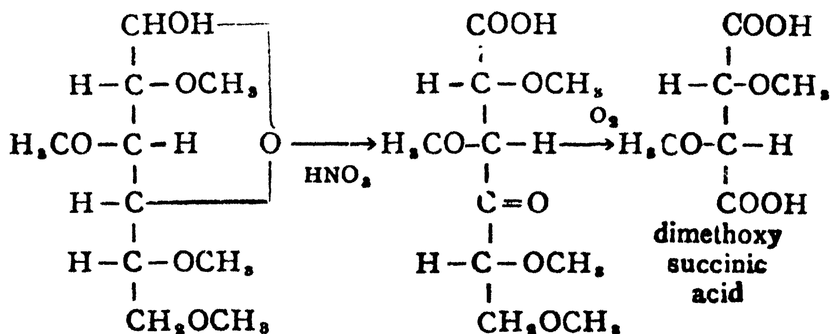


D-glucose *D*-glucuronic acid *D*-xylose

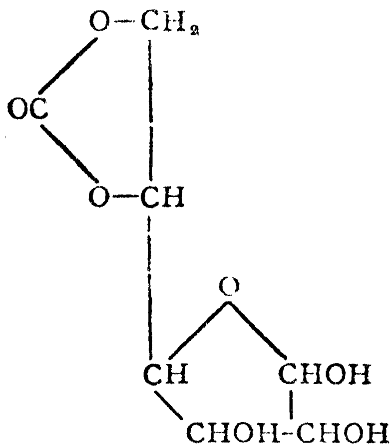
It is now believed that pentoses are not the *primary* products of photosynthesis, but are derived from the hexoses, as xylose is from glucose.

γ-SUGARS OF FURANOSES :—In addition to the α and β methyl glucosides, a third isomeric methyl glucoside was reported by Fischer; glucose was made to react at room temperature with dry methanol containing 1% HCl gas. He termed it γ-methyl glucoside. It showed great instability toward acids, and was completely inert toward maltase and emulsin. Hence it probably differed from the α and β isomers in the size of the ring present in the molecule. This was followed by Irvine's isolation of a new isomeric tetra-methyl glucose.

These results have been recently confirmed by Haworth and others. They have reported that on methylation and subsequent hydrolysis the γ-methyl glucoside gives a tetra-methyl glucose differing from the crystalline compound derived from the α and β methyl glucosides. With bromine water it gives a tetra-methyl glucono-lactone. The latter is a crystalline compound and is slowly hydrolysed by water and thus resembles a γ-lactone. Further the tetra-methyl glucose (obtained from the γ-methyl glucoside) on oxidation with concentrated nitric acid gives dimethoxy succinic acid :—



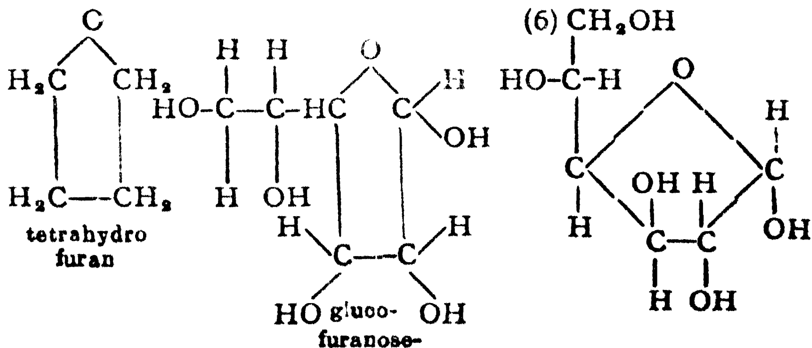
The results indicate that the γ derivatives have the butylene oxide or 1·4 structure. The above conclusions have been subsequently confirmed by other chemists. But, so far, the free γ-sugar has not been isolated. It represents an extremely active form which readily passes into the more stable δ-form. However, many derivatives of this γ-sugar have been isolated by Haworth and Porter. Recently, the following crystalline carbonato-derivative of γ-sugar has been obtained by them.



Carbonate derivative of γ-sugar

Also, the ∝ and β methyl glucosides derived from the γ or 1·4 structure have been now obtained through the corresponding 5·6 carbonate, 2, 3 diacetates. They do not reduce Fehling's solution and are not affected by dilute $KMnO_4$.

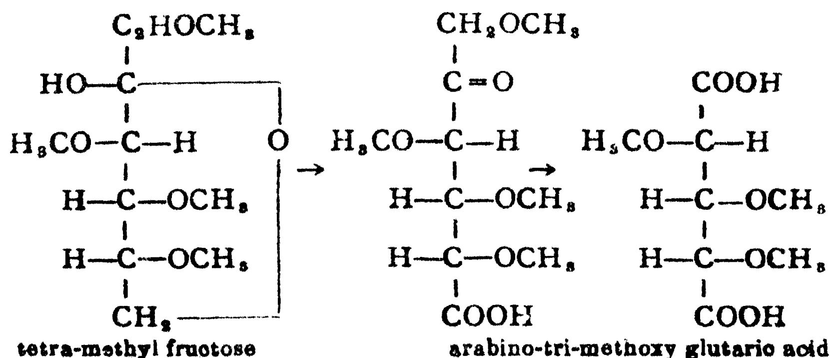
Haworth terms this labile or γ sugar as *furanose i. e*, a compound related to tetra-hydrofuran and represents it by the following formula :—



Thus, the ***normal*** sugars are related to ***pyran*** and are derived from it and are called δ sugars. The labile or γ sugars are similarly related to ***furan*** and are its corresponding hydroxy derivatives. Thus, there are two series of sugars: (*i*) those related to the ordinary α and β methyl glucosides and which possess the *pyranose* structure; and (*ii*) those related to Fischer's γ-methyl glucoside which contain the ***furanose*** structure. In the ***pyranose*** ring, the oxygen atom makes a valence angle of 90° which is equal to the normal valence angle of oxygen atom, while in the *furanose* structure, the valence angle of oxygen atom, is 150°. Thus, the *pyran* ring is less strained and more stable than the *furan* ring. The γ sugars are also termed hetero sugars or *h*-sugars. Thus, it has been experimentally established that *D*-glucose and other aldo- hexoses are capable of existing as *pyranoses* and *furanoses*. The isomeric keto-hexoses, *i. e.*, *D*-fructose etc. are also known to exist in two ring forms. We shall, now, discuss the relevant experimental evidence that has been brought forward to establish the pyranose and furanose structures for *D*-fructose.

Ring Structures for Fructose

We have assigned an open chain structural formula for *D*-fructose. Fructose, like glucose, shows mutarotation; it also gives two isomeric crystalline methyl-fructosides with CH_3OH and HCl gas. But the α and β fructoses have not been so far isolated. The ordinary compound is the β-isomer. On further methylation, the tetra-methyl-fructoside is obtained. The latter on hydrolysis gives a crystalline tetramethyl-fructose derivative. All these reactions suggest a ring structure for *D*-fructose in analogy to glucose. The experimental evidence for the **pyranose** ring in the fructose molecule is as follows; the tetramethyl-fructose (crystalline) on oxidation with HNO_3 is converted into an acid (The CH_2 OCH_3 → COOH). The latter on oxidation with $KMnO_4$ gives a δ-lactone which on further oxidation gives arabino-trimethoxy-glutaric acid.

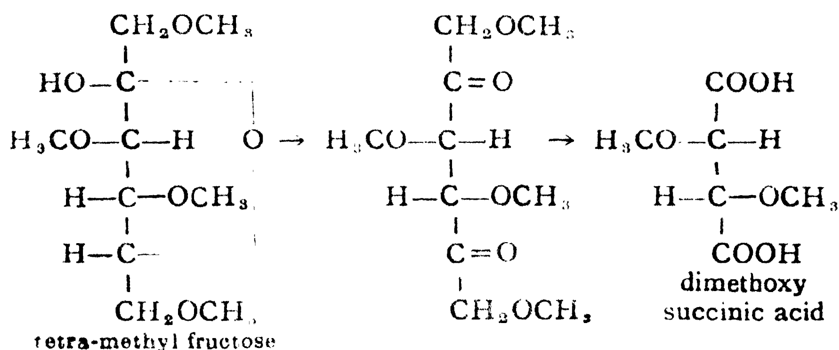


tetra-methyl fructose arabino-tri-methoxy glutaric acid

These results indicate that C_2, C_4 and C_5 cannot be involved in the ring formation and hence the presence of the δ-oxide ring—pyranose

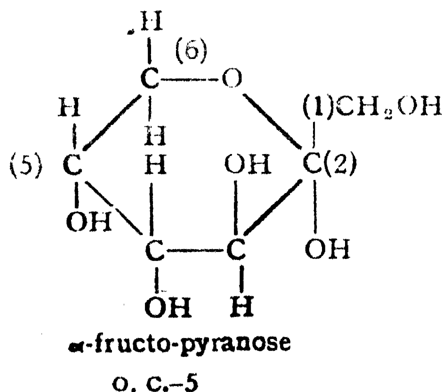
structure—in the fructose molecule is indicated (If the the ring present were 1 : 4, the three-step oxidation of the tetramethyl fructose derivative would *not* give a dibasic acid containing five carbon atoms).

FURANOSE STRUCTURE FOR FRUCTOSE :—Octa-methyl sucrose obtained by the methylation of sucrose, on acid hydrolysis, gives an equimolar mixture of tetra-methyl glucose and tetra-methyl fructose. The fructose derivative is isomeric with the tetra-methyl fructose obtained directly from fructose by methylation and hydrolysis. It is also obtained as a much purer product, by the hydrolysis of heptamethyl sucrose. On oxidation with nitric acid, it gives *l*-dimethoxy succinic acid :—

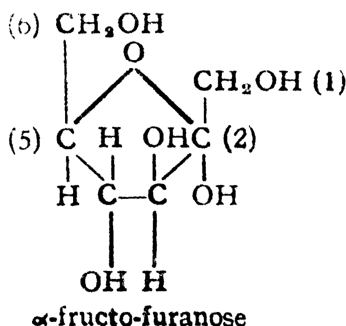


These results show the presence of a γ-oxide ring in the molecule. Hence it follows that fructose residue in cane-sugar possesses the *butylene oxide or furanose* structure. Like the gluco-furanose, the fructo-furanose is extremely reactive and has so far not been isolated in the free condition, but is only known in the form of its derivatives *e.g.* cane-sugar, inulin etc.

The hexagonal and pentagonal formulas for the pyranose and furanose structures respectively for *D*-fructose are :



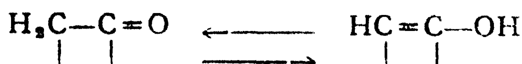
α-fructo-pyranose



α-fructo-furanose

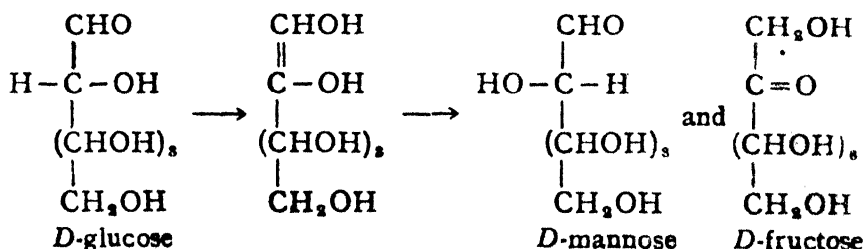
More recent researches in this field have revealed the presence of structures, other than five or six-membered ones, in the derivatives of the natural hexoses. Some of these structures will be briefly discussed here.

ENOLIC STRUCTURES FOR THE SUGARS—The hexoses (glucose, mannose and fructose) contain a free or potential carbonyl group. One of the characteristic reactions of the group is the tendency to enolise:—



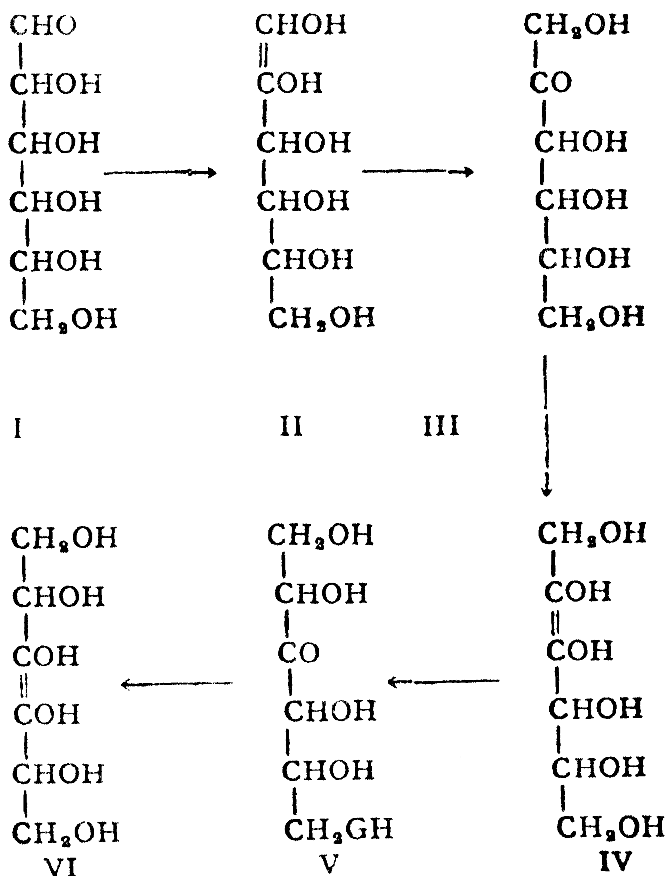
The extent and degree of enolisation is determined by many structural factors and influenced by surrounding conditions. Thus alkalinity is found to favour the enolisation of many aldehydes and ketones. In the case of the sugars, there is evidence for the existence of enolic structures especially in alkaline solutions. Lobry de Bruyn's observation that in presence of dilute alkali, glucose is partly converted into mannose and fructose, is satisfactorily explained on the basis of an ene-diol structure for the glucose molecule.

Recently, Lewis and others have carried out extensive investigations on the inter-conversions of the sugars and their methyl derivatives. They found that with tetra-methyl glucose, the tetra-methyl mannose is formed, but no ketose formation takes place. As a result, they have proposed that the mechanism of the change involves simple enolisation of the sugar molecule:—

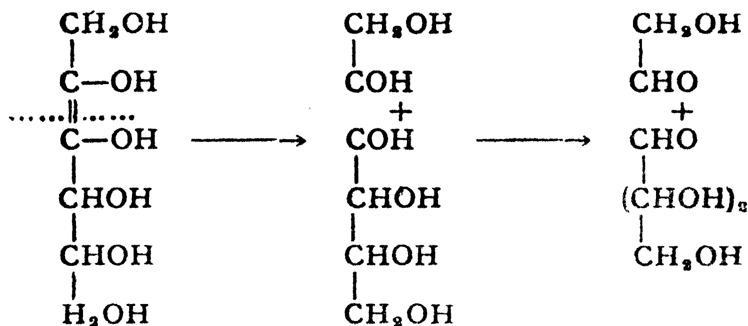


In the case of the methylated sugar, enolisation is precluded because of the immobility of the methoxy groups and hence, no ketose formation is possible.

Evance and his collaborators have investigated the action of alkalies on sugars under more drastic conditions. Their researches have indicated that the changes involved are deep-seated and can be satisfactorily accounted for by assuming enolic structures for the sugar molecules. The double bond generated by the enolisation of the molecule migrates further down the carbon chain from the aldehydic end as given below:—



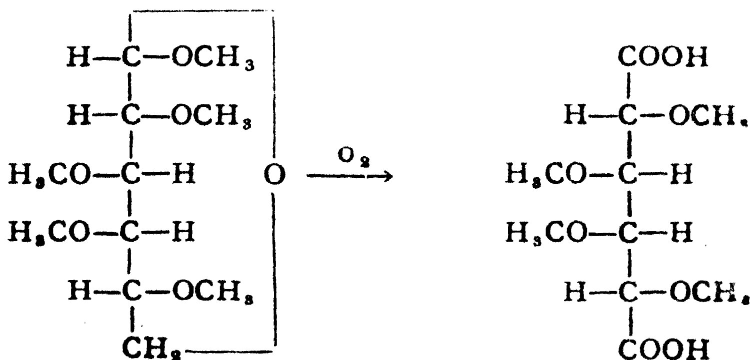
The deep-seated changes are brought about by the cleavage of the *ene-diol structure* at the point of the double bond. The rupture is shown below by a dotted line.



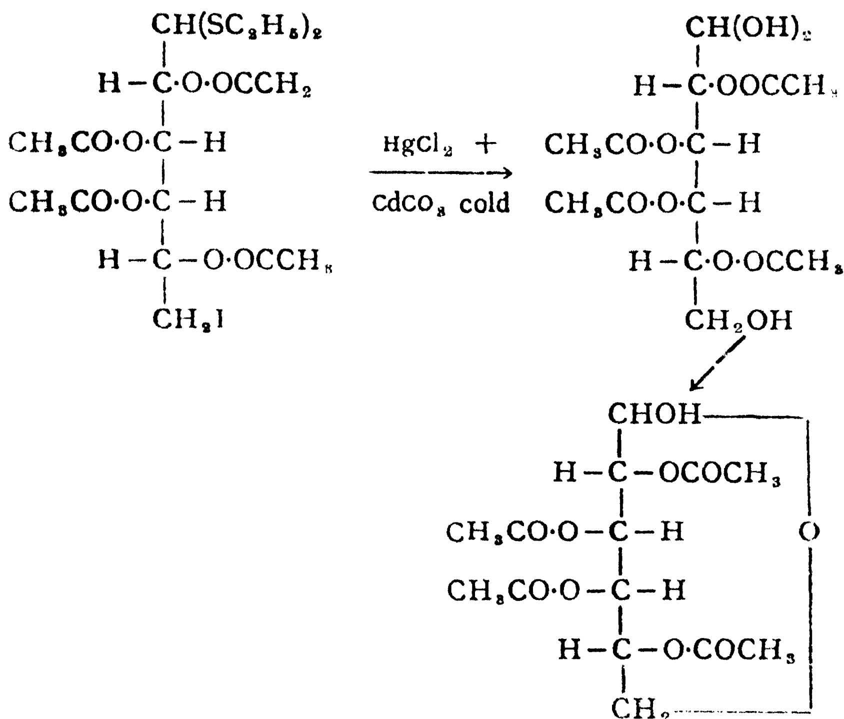
It is to be noted that for the formation of the *ene-diol structure*, an acyclic or aldehydic open chain form for the sugar molecule has been assumed as an intermediate. The actual presence of such a carbonyl group is sufficiently indicated by Marchlewaski's experiments. He has reported that an absorption band for the *CO* group actually appears on the addition of alkali to the sugar solution, and disappears when the alkali is neutralised. There is also indirect chemical evidence for the existence of the acyclic form. The cyanohydrin reaction of the sugars takes place only in slight alkaline conditions with the acyclic form of the sugar.

Other Structures

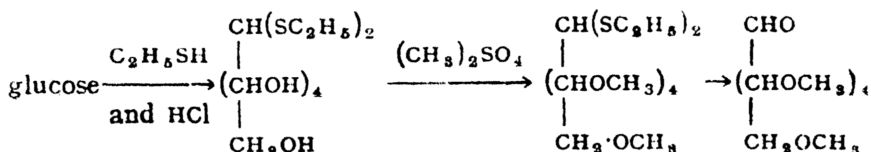
1 : 6 'RING STRUCTURE:—*D*-Galactose was converted by Michael and others into a pentamethyl derivative which by oxidation reaction was proved to have 1: 6 ring structure.



The seven-membered ring system has been termed *septanose*. A corresponding tetra-acetyl septanose has been synthesised by them, n the following way:

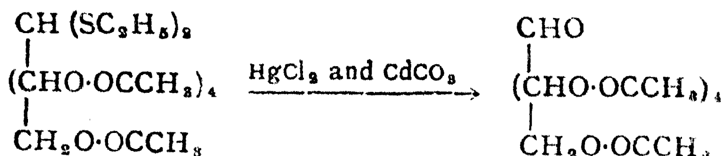


OPEN CHAIN STRUCTURE:—We have seen how the lactol formulas for the sugars have been developed and are based on sufficient experimental evidence.. It was greatly exciting when in 1926 Levene and Meyer announced the isolation of penta-methyl glucose with an open-chain structure. The aldehydo-sugar derivative (as it was called) was synthesised by them from glucose ethyl-mercaptal as follows:—



This aldehydo-pentamethyl glucose readily gives the acetal with CH_3OH and HCl gas, while ordinary glucose gives only the semi-acetal.

Wolfrom had greater success in obtaining a crystalline aldehydo, penta-acetate of glucose. He carried out the hydrolysis of the acetylated glucose ethy-mercaptal in dilute acetone solution with mercuric chloride in the presence of cadmium carbonate.



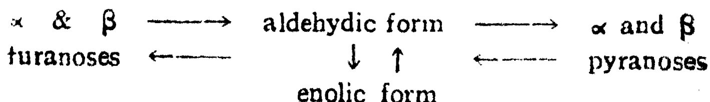
This compound gives the Schiff's test and readily forms a semi-carbazone (Ordinary glucose does not give the Schiff's test). It also exhibits muta-rotation in methanol solution. This penta-acetyl derivative is not identical with the one obtained by direct acetylation of glucose. This indicates that the latter does not contain a free CHO group.

Aldehydo-acetate forms of other sugars, e.g., galactose and mannose have been obtained. P. Brigl has isolated the aldehydo-glucose as a penta-benzoyl derivative by an analogous method Thus, so far, only acetyl or benzoyl derivatives of the aldoses with a free aldehyde group have been prepared. A free aldehydo-sugar, however, has not been isolated.

KETO-STRUCTURE FOR *D*-FRUCTOSE :—As far back as 1915, Hudson and Brauns had obtained a penta-acetate by direct atetylation from fructose. It was pointed by Pace and Rich that it contained an open chain structure. The carbonyl group in the molecule, however, showed decreased reactivity.

Thus the open-chain structure has been demonstrated both in aldo and keto-hexose derivatives. The free hexoses are probably incapable of existence in the aldehydo-or keto-forms. On the other hand in the case of the acetyl derivatives, as the hydroxyl groups are masked, the possibility of a ring formation is totally excluded and hence, free *CHO* or *CO* group may be present in such derivatives.

Summing up, it is obvious that *D*-glucose or any other sugar, is a highly tautomeric compound existing in six different structural forms:



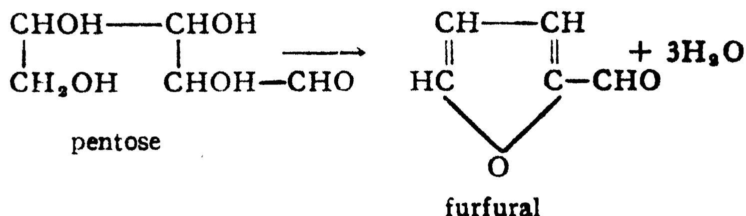
The aldehydic form cannot be detected by ordinary chemical methods. However, the solution of sugars in 50% H_2SO_4 exbibits an absorption band in the U. V. which is characteristic of a CO group. Similarly evidence has been obtained by Brigl and others, for the existence of tautomeric forms in the case of *D*-fructose. They

have isolated and identified three crystalline benzoates, with a pyranose, furanose and an open-chain structure.

PENTOSES

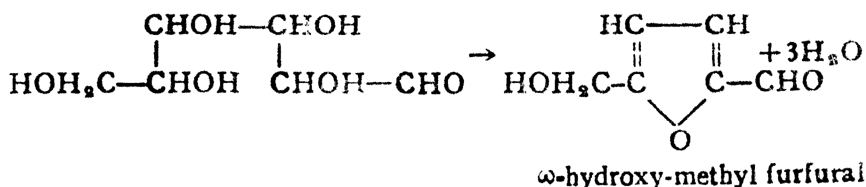
OCCURRENCE :—The pentoses do not occur in the free condition in nature, but are widely distributed as the complex condensation products—the pentosans or the natural gums. The pentosans occur in wood and, thus, constitute the chief structural material of all plants and trees. They are not hydrolysable by enzymes and hence, cannot be readily utilised by animals as food Other sources of pentosans are the lichens, the natural resins and the moulds. One of the pentose, ribose, occurs as a constituent of nucleic acids, of pancreas, of liver and of vitamin B complex.

GENERAL COMPOSITION AND BEHAVIOUR: The pentoses are obtained by hydrolysis from the pentosans. They possess the molecular composition $C_5H_{10}O_5$. Structurally they are polyhydroxy-aldehydes *i.e.*, they are aldoses; (keto-pentoses are unknown in nature). They give all the reactions characteristic of the mono-saccharoses. Thus they can be readily oxidised to monobasic acids, which can be reduced or epimerised like gluconic acid, They can be degraded by the methods of Wohl and Ruff to tetroses. On boiling with dilute acids e.g. 12% HCl they are converted into *furfural* (furfuraldehyde).



Furfural gives characteristic colour reactions which are used as tests for pentoses. Thus with aniline acetate paper, vapours of furfural give a red colouration. With phloroglucinol, furfural gives a condensation product which is sparingly soluble and is litharge-coloured; its composition is $C_{11}H_{12}O_6$. This reaction is made the basis of a quantitative estimation of pentoses.

The hexoses on boiling with mineral acids are changed into ω-hydroxy-methyl furfural, which on further heating with acid under pressure gives levulinic acid.

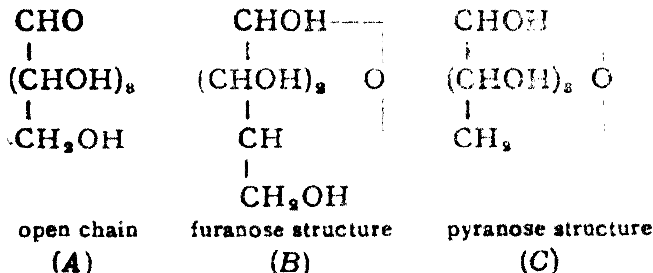


ω-hydroxy-methyl furfural

INDIVIDUAL PENTOSES:—The most important and most common pentoses are *D*-xylose and *L*-arbinose. The other members are *D*-ribose and *D*-lyxose. *D*-Xylose is found as the pentosan, xylan, widely distributed in nature. It is also known as wood sugar. A modern commercial source of this sugar is the cotton-seed hull bran.

The vegetable gums, like gum arabic, contain the pentosan, araban. On acid hydrolysis, they give *L*-arabinose. Another source of *L*-arabinose is the sugar from beet residues

STRUCTURAL AND CONFIGURATIONAL RELATIONSHIPS:—The pentoses have been shown to possess like the hexoses, an open-chain structure (*A*) and the lactol structures (*B* and *C*).



open chain (*A*) furanose structure (*B*) pyranose structure (*C*)

These structures are based on experimental evidence similar to that led in the case of the hexoses (glucose). They give a tetra-acetyl derivative; they give an oxime, a hydrazone and a monobasic acid and finally a dibasic acid *i.e.* tri-hydroxy-glutaric acid on oxidation; they also show mutarotation. Thus an aldo-pentose possesses a pyranose and a furanose structure. Further, each exists in α and β forms. The configurational relationships have also been studied. The pentoses, *D*-arabinose, *D*-xylose, *D*-ribose and *D*-lyxose have been assigned the respective configurations, by methods that have been discussed earlier.

D-XYLOSE OR WOOD SUGAR:—It is obtained from wood and cotton-seed hull bran by boiling them with dilute mineral acids.

The latter contains 25-30 per cent of xylan. The commerical possibilities of xylose are:—(*a*) it can be used in the spinning of rayon-fibre to give liquid of proper consistency, (*b*) on oxidation, it is converted into tri-hydroxy-glutaric acid which may replace citric acid in the manufacture of beverages, and lactic and acetic acids in tanning and dyeing industries, (*c*) the nitro derivatives of xylose can find extensive application as explosives, lacquers and plastics.

FURFURAL :—This is the least expensive of all the aldehydes now prepared. It is commercially produced cheaply from corn stalks or oat hulls. It can be used as :—(*a*) a paint remover in the modern spray painting industry, (*b*) a substiture for formaldehyde in the preparation of synthetic plastics and tanning material, and (*c*) a motor fuel as a substitute for petrol. It is an oil (b. p. 162°)

L-ARABINOSE :—It is obtained by hydrolysis of gum arabic or cherry gum.

SUGAR DERIVATIVES

HYDRAZONES :—The hexoses react with phenylhydrazine in two ways to give (*a*) mono-hydrazones and (*b*) di-hydrazones or osazones. Both these types of derivatives are important and have found, as already mentioned, many applications in the chemistry of sugars.

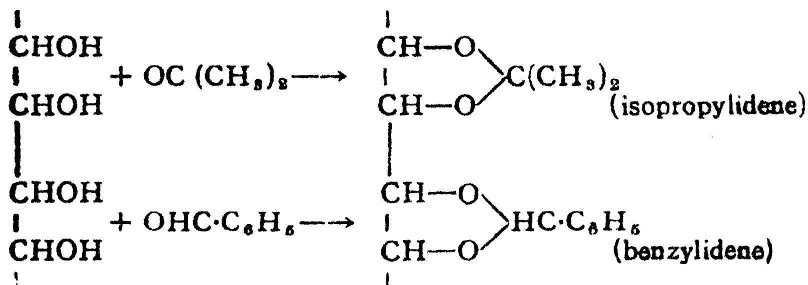
The phenyl hydrazones of the reducing sugars are usually soluble in water : but that of mannose is sparingly soluble and hence it can be used to separate mannose from mixtures. Recently, the substituted phenyl hydrazines : *p*-bromo, *p*-nitro, and 2, 4 dinitro phenyl hydrazines have been used for the characterisation and identification the reducing sugar. Naphthyl-hydrazines have also found some applications.

The osazones are formed with excess of the reagent. On heating with a dilute acid or with an aldehyde like C_6H_5CHO, the osazones give α-keto-alde-hydes called *osones*. The latter on reduction with zinc and acetic acid give the corresponding 2-ketoses.

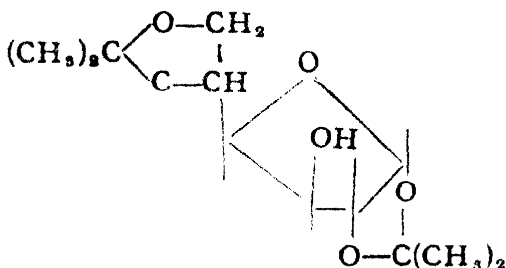
ACETONE SUGARS :—Sugars like glucose and mannose combine with one or two molecules of acetone or benzaldehyde to yield isopropylidene and benzylidene derivatives respectively. The acetone derivatives formed by shaking the sugar with acetone containing a little H_2SO_4 or HCl or $CuSO_4$. The benzylidene derivatives are obtained by heating the sugar with benzaldehyde in presence of

anhydrous $ZnCl_2$. They are usually crystalline compounds stable to alkalies but rapidly attacked by dilute acids.

THE STRUCTURES OF ACETONE DERIVATIVES :—It was first assumed that two hydroxyl groups in *cis* position are involved in the condensation with the acetone or benzaldehyde molecules.



The acetonisation is also accompained by a change in the size of the ring. Thus gluco-pyranose, on acetonisation gives only a diacetone derivative 1, 2, 5, 6 diacetone gluco-furanose.



Diacetone gluco-furanose.

In recent years, the structures of the mono and diaceton glucose have been thoroughly investigated by many chemists. (Irvine and Scott, Levene and Meyer, K. Freudenberg and Doser, Charltone, Anderson and Haworth). Accordingly, it is now established that *(i)* in mono-acetone glucose, the acetone group is condensed with C_1 and C_2 and the lactol ring is a furanose one ; *(ii)* in the diacetone glucose, positions 1 and 2 carry an acetone group. The *OH* group in position 3 is free and C_4 is involved in the lactol ring formation. This places the second acetone group on C_5 and C_6. In the diacetone derivatives the acetone residue attached to C_1 and D_2 is more firmly held than the other ones. Thus on treatment with 1N–HCl, 1, 2, 5, 6, diacetone-glucofuranose gives 1, 2 mono-acetone-furanose.

These proofs are independent of the assumption that only *cis* hydroxyl groups are invoved in the condensation with the molecules of acetone. The acetone sugar is converted into methylated sugar whose structure is then established by oxidation methods (Haworth and others). It is to be noted that during the formation of these acetone sugars, the size of the ring undergoes a change. Thus, a shift from pyranose to furanose structure takes place in the case of glucose, mannose and xylose.

APPLICATIONS OF THE ACETONE SUGARS :—Irvine and Scott have employed these acetone sugars in the preparation of partly methylated sugars with the methyl groups in known and definite position, which have served as reference compounds in the investigation of the structure of disaccharoses. The acetone groups block some of the *OH* groups while others are free. The free hydroxyl groups are then methylated by the usual methods and the acetone groups subsequently removed by hydrolysis to give the partly methylated sugars. In this way, mono-, di-, and tri-methyl glucoses have been obtained. The method has been extended to the preparation of partly methylated mannose and fructose derivatives.

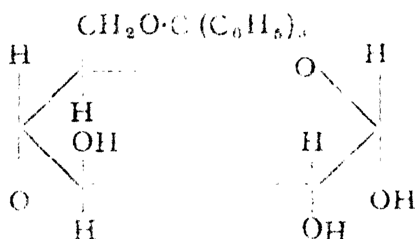
CARBONATE SUGARS :—Allpress and Haworth have obtained what are called the carbonate derivaties of sugars. Glucose reacts with $COCl_2$ in presence of a weak base like pyridine to form the carbonate derivative. Probably two hydroxyl groups in *cis* position take part in the reaction. Haworth has synthesised 5-6 carbonato, 1-2-acetone glucose, by the interaction of mono-acetone glucose and phosgene ($COCl_2$). The carbonate sugar is stable to dilute acids but rapidly hydrolysed by alkalies. Haworth and Porter have obtained crystalline di-carbonates with two equivalents of $COCl_2$ in pyridine. They resemble the corresponding di-acetone derivatives, but are less readily attacked than the latter by dilute acids; alkalies however completely hydrolyse them. Mannose, galactose and fructose have also been converted into crystalline carbonato derivatives.

Under certain experimental conditions, the sugars react with $Cl\text{-}COOC_2H_5$ to give the carbo-ethoxy-derivative, the H of the OH being replaced by $-COOC_2H_5$.

ALKYL SUGARS :—A large number of alkyl derivatives of the

sugars have been prepared. These include *(i)* the mono alkyl sugars e. g. mono methyl or ethyl glucoside, mannoside etc., *(ii)* the poly alkyl derivatives like tetramethyl glucose, tetramethyl fructose etc. Their mode of formation and properties have been discussed earlier. They have played an important role in the elucidation of the structures of glucose and other sugars. Our knowledge of the more complex carbohydrates rest on the results of investigation of their methyl derivatives. Perhaps, a more fruitful reagent has not yet been discovered in sugar research.

TRIPHENYLMETHYL OR TRITYL ETHERS :—The sugar e. g. glucose, galactose, and the glucosides also react with $(C_6H_5)_3C{\cdot}Cl$ in pyridine solution, to give the trityl ethers. In these reactions, the primary alcoholic group (CH_2OH) is preferentially etherified. Thus we have from glucose :



The group (trityl) can be readily and quantitatively removed, even at room temperature, with a saturated solution of HBr in glacial acetic acid. It can also be removed by catalytic hydrogenation. This has a great practical advantage Hence the trityl ethers have found some synthetic applications : (*a*) the synthesis of 6-mono methyl glucose, and (*b*) the synthesis of partly methylated sugars.

ACETYLATED SUGARS :—The OH groups in the sugar molecules are protected by acetylation. The acetylation is carried out by using :

(*a*) $(CH_3CO)_2O$ and fused Na-acetate at high temperatures ;

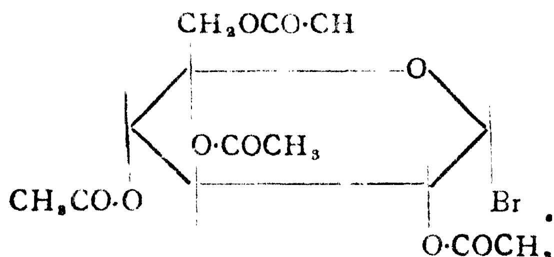
(*b*) $(CH_3CO)_2O$ and fused $ZnCl_2$;

(*c*) $(CH_3CO)_2O$ and pyridine at ordinary temperature :

(*d*) $(CH_3CO)_2O$ and a small quantity of H_2SO_4.

The derivatives are usually crystalline compounds. An important application is in the preparation of aceto-halogen sugars.

Aceto-bromo-glucose or tetra-acetyl-α-glucosyl 1-bromide is an important aceto-halogenose. It was first obtained by Koenigs and Knorr by the action of actyl bromide on glucose. Later on, Fischer devised the more elegant method for preparing the acetohalogen sugar compounds. It consists in treating the hexose acetate dissolved in glacial acetic acid with the appropriate halogen acid, in this way, the chloro,-bromo-, and iodo-aceto-sugars have been obtained; the corresponding aceto-fluoro-derivative has been synthesised by Brauns. Recently, Scheurer has developed the following method for the preparation of α aceto bromo glucose: Br_2 is added to red phosphorus suspended in glacial acetic acid; glucose or its penta acetate is then added to give a good amount of the aceto bromo glucose. The aceto bromo-glucose has the structure—

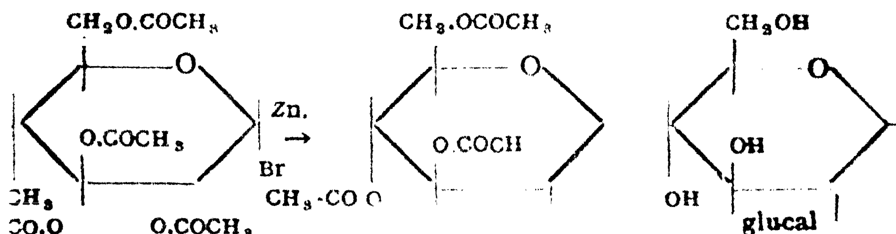


It has found extensive use in the preparation of (*i*) glycosides, disaccharoses, (*ii*) glycals (*iii*) desoxy-sugars and (*iv*) glycoseens.

(*i*) SYNTHESIS OF GLYCOSIDES, DISACCHAROSES :—The Br atom is very reactive and undergoes condensation with hydroxylic compound in pyridine or benzene solution, and in presence of Ag_2CO_3. If the hydroxylic compound is a non-sugar, a glycoside is formed; on the other hand, a disaccharose is obtained if the hydroxylic compound is a sugar molecule. The glycoside obtained is always the β-isomer. If Hg acetate is used in place of silver carbonate as the condensing Agent the corresponding α-isomer is obtained. A recent modification consists in the use of anhydrous $CaSO_4$ and iodine as the condensing agent, with improved yields.

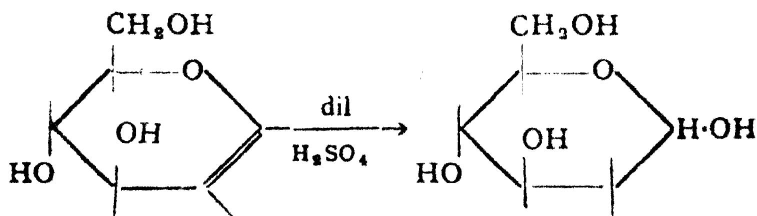
(*ii*) SYTHESIS OF GLYCALS :—Aceto-bromo-glucose on treat-

ment with Zn and acetic acid loses a molecule of CH_3COBr and yields an unsaturated glucose derivative: on deacetylation glucal is formed.



Other aceto halogenoses, on similar treatment give rise to corresponding unsaturated sugar derivatves (with a double bond between C_1 and C_2 called in general *glycals*.

(*iii*) SYNTHESIS OF DESOXY SUGARS :—The glycals on treatment with dilute H_2SO_4, are converted into 2-desoxy sugars *i.e.*, the CHOH group in position 2, is replaced by CH_2. Thus glucal yields 2-desoxy-glucose.



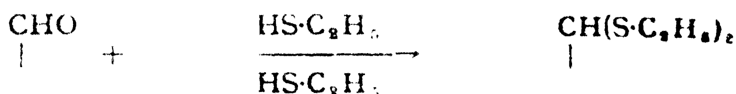
Further glucal on treatment with perbenzoic acid and water gives D mannose.

Lastly it may be mentioned that glucal on treatment with ozone gives D-arabinose; thus we have a method of degrading a hexose into a lower hexose.

(*iv*) SYNTHESIS OF GLYCOSEENS :—The aceto bromo glucose, on treatment with diethylamine, loses a molecule of HBr and a new type of unsaturated derivative of glucose is formed, which on deacetylation yields glucoseen.

BENZOYLATED SUGARS :—A number of methods have been devised for the preparation of benzoylated sugars. Kueny obtained the first benzoylated sugars by the action of C_6H_5COCl on the sugars, in the presence of alkali. This method, however gave a mixture of partly benzoylated sugars. Fischer and Freudenberg could obtain completely benzoylated products by replacing the alkali by quinoline. Pyridine was also found to greatly improve the yields. Mono-acetone glucose was thus benzoylated and selectively hydrolysed with HCl to remove the acetone groups and to form the tri-benzoyl derivative. It was Schlubach and Huntenburg who obtained the two isomeric penta-benzoates from these partially benzoylated compounds.

MERCAPTALS :—Aldoses react with C_2H_5SH and $C_6H_5CH_2\cdot SH$, in presence of con. HCl, to form the corresponding mercaptals. Under these conditions, ketoses do not react at all.



$$\begin{matrix} CHO \\ | \end{matrix} + \xrightarrow[HS\cdot C_2H_5]{HS\cdot C_2H_5} \begin{matrix} CH(S\cdot C_2H_5)_2 \\ | \end{matrix}$$

Demerecaptalation is readily effected by treatment with aqueous $HgCl_2$ and $CdCO_3$. These reactions have found an important application (see p. 69) in the preparation of acyclic aldehydo-sugars.

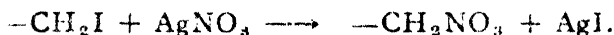
TOSYL DERIVATIVES :—*p*-Toluene sulphonyl chloride (called tysyl chloride) reacts with OH groups, in pyridine solution and at ordinary temperature. The time required however is much longer than required for acetylation or benzoylation. Further, the hydroxyl groups in different positions react at different rates ; especially the OH group on C_6 reacts much faster than other hydroxyl groups. This has enabled to obtain some special derivatives of sugar. The other important applications of tosyl sugars are : (*i*) the preparation of nitrate sugars, (*ii*) the preparation of methyl (desoxy) sugars and (*iii*) the preparation of ethylene oxide sugars.

(*i*) NITRATE SUGARS :—The tosyl group–CH_2.O.Ts, on heating with NaI in acetone at 100°C for 2 hours, is converted into an iodo-hydrin.



$$—CH_2O\cdot Ts + NaI \longrightarrow —CH_2I + NaO—Ts.$$

The iodo-hydrin on heating with $AgNO_3$ gives the nitrate sugar, and silver iodide, which can be quantitatively estimated.

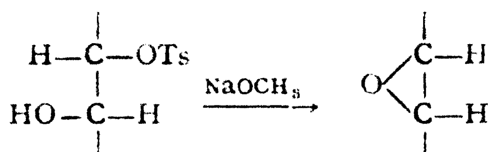


$$-CH_2I + AgNO_3 \longrightarrow -CH_2NO_3 + AgI.$$

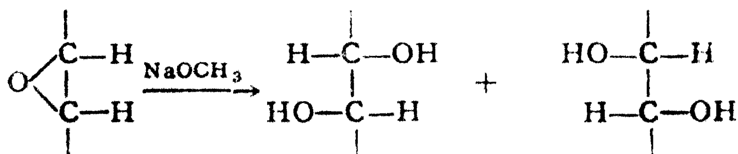
The–CH·O–Ts groups, on the other hand are known not to suffer such replacement reactions. Hence this affords, a simple method of determining quantitatively, the number of free CH_2OH groups in a compound containing both the primary and the secondary alcoholic groups.

(*ii*) METHYL SUGARS :—The iodohydrins can be reduced with zinc and acid to CH_3. In this way, a 6-methyl (desoxy) sugar, can be synthesised. A tosyl group, however on C_1 of the ketoses, cannot be replaced by I as above, with NaI in acetone.

(*iii*) ETHYLENE OXIDE SUGARS :—These derivatives are obtained by the hydrolysis of the tosyl derivatives by the action of $NaOCH_3$ in the cold. One of the conditions for the formation of such a derivative is that an OH group *trans* to the tosyl group exists on the α carbon atom ;

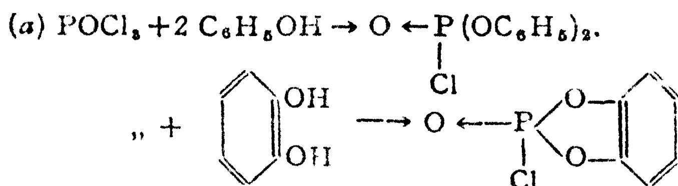


the transformation is accompanied by a Walden Inversion. The ethylene oxide derivatives possess a special interest. On treatment with alkali, the ring opens up, a Walden Inversion occurs and two products which are epimeric are obtained. Thus the above series of reactions affords a method of inverting the configuration of asymmetric carbon atoms in the molecule.



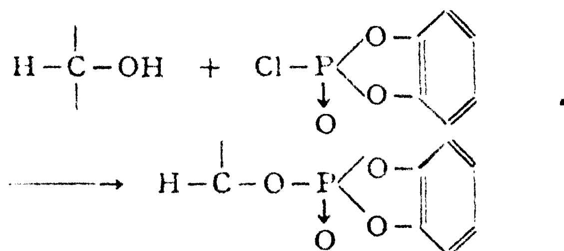
SUGAR PHOSPHATES:—They are the constituents of nucleic acids from the cell nuclei and are widely spread in nature. They play an

important role in fermentation and in other meta-bolic changes. They are prepared by three methods. They are—(1) the action of Ag_3PO_4 on the aceto-bromo-aldose; in this way, the 1-phosphates are obtained; (2) the action of an ester of chlorophos-phonic acid, which is usually prepared from a phenol and $POCl_3$.



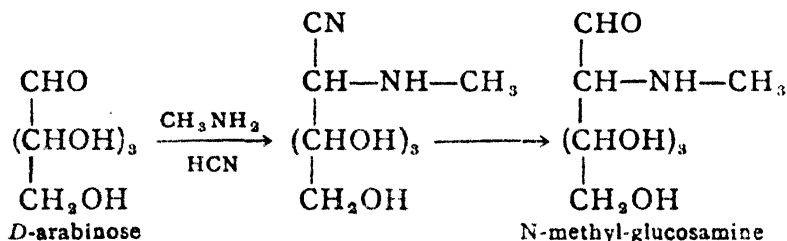
The catechol-chlorophosphonate is easier to prepare; further the removal of the catechol residue is also relatively easier.

(*b*) The chlorophosphonates are then used in pyridine solution to obtain the phosphate sugar.



On hydrolysis or hydrogenolysis, the aryl residues *i. e.* catechol residue is removed and the sugar phosphate is formed; (3) Distilation with phosphoric acid; this gives usually the 6-phosphates.

AMINO-SUGARS:—They are derived from a monosaccharose by replacing an OH with an NH_2 group. Chitin is a natural source of amino sugars. The most common amino sugars are the 2-amino-*D* aldoses; 2-amino-glucosamine is obtained from chitin by acid hydrolysis. Its constitution has been established by a synthesis of its N-methyl derivative:

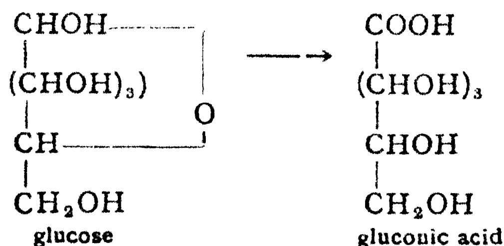


6-Amino-glucosamine has been synthesised by Fischer and Zach; 6-bromo-tri-acetyl-methyl-glucose was treated with NH_3 and subsequently hydrolysed. Fructosamine (1-amino fructose) is obtained by reduction of glucosazone, with Zn dust and acetic acid in alcohol. Catalytic reduction, gives better yields.

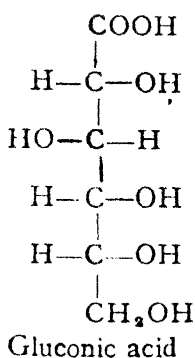
Oxidation Products of Sugars:—A hexose which is a polyhydroxyaldehyde gives rise to a number of oxidised structures containing the same number of carbon atoms. Thus, we have:—

(*i*) Monobasic acids—the aldonic acids, (*ii*) dibasic acids, (*iii*) the glycuronic acids.—the aldehydic-acids, (*iv*) the keto acids and (*v*) the keto-aldehydes—the osones.

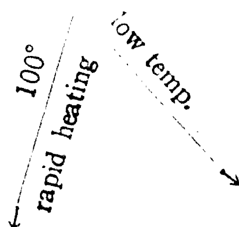
(*i*) THE ALDONIC ACIDS:—They are readily obtained from the aldose by mild oxidation with bromine water or with hypobromite ion (Isbell).

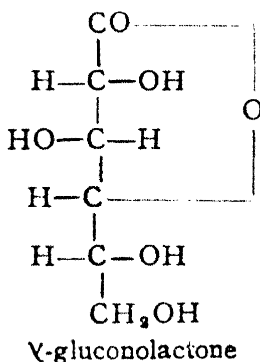


Some of the characteristic reactions of an aldonic acid are (*a*) ease of reduction with sodium amalgam to the corresponding aldose (*b*) conversion by heating with pyridine or quinoline into its epimer; both these reactions have found very fruitful applications in sugar chemistry, (c) formation of the lactons: the same aldonic acid gives rise to two different lactones—γ and δ depending upon the mode of formation. Thus, rapid heating of the acid at 100° converts it into the γ-lactone, while the δ-lactone results from heating the acid at a lower temperature and for a longer time. The γ-lactone is more stable than the δ-lactone.

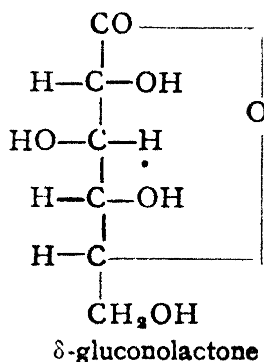


Gluconic acid



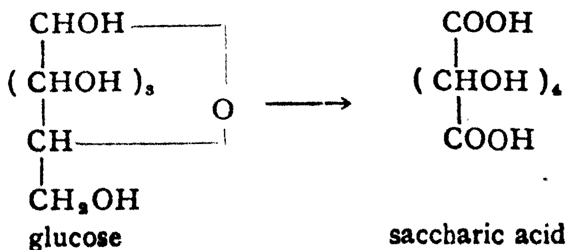


γ-gluconolactone



δ-gluconolactone

(*i*) DIBASIC ACIDS :—These represent the product of vigorous oxidation of the aldose molecule; both the terminal carbon atoms appear as *COOH* groups.



glucose saccharic acid

Similarly, mannose gives manno-saccharic acid and galactose gives mucic acid. They are crystalline compounds which are either optically inactive or active depending on the symmetry or dissymmetry of the molecule. Such properties have been employed by Fischer to establish the internal configurational relationships between the aldoses.

(*iii*) GLYCURONIC ACIDS :—This is the general name for the aldehydo-carboxylic acids (-uronic acid) derived from the aldoses. They are formed as a result of the oxidation of hexoses in the body, when the primary alcoholic group undergoes preferential oxidation to - *COOH*. The specific names are :—

(*a*) Dglucuronic acids from Dglucose,
(*b*) Dmannuronic acid „ Dmannose,
(*c*) Dgalacturonic acid „ Dgalactose.

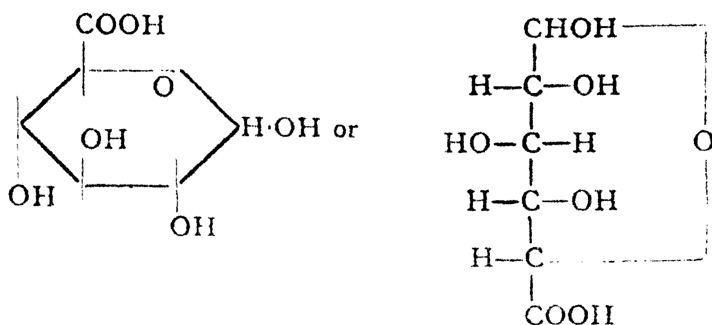
The uronic acid may be prepared by the oxidation of the glycosides; oxygen in presence of Pt is used as the oxidising agent. Nitrogen peroxide is also an efficient oxidising agent.

In their general properties, they resemble the parent sugars. They show reducing action and can form glycosides. The COOH group can be esterified and forms salts with bases like cinchonine, brucine; the latter salts have been used for identification. They readily suffer decarboxylation on boiling with HCl (19%) and are converted into furfural. Tollens and Lefevre have developed a method for their quantitative estimation, based on the estimation of CO_2 evolved.

The glycuronic acids are widely distributed in nature. Thus glucuronic acid is the constituent of many Plant gums, such as gum arabic, damson gum etc., and of heparin, the anti-coagulant in the blood. The pectic acid-the constituent of pection- is built up of galacturonic acid units, and the building unit of the seaweed polysaccharose, alginic acid is mannuronic acid.

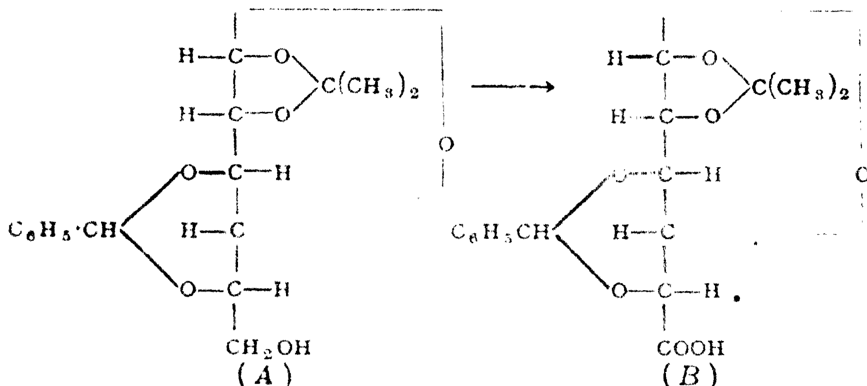
D-Glucuronic acid is found in human urine as phenolglucuronic acid. Recently, it has been discovered as a constituent of the sugar portion of muco-proteins. It readily forms a crystalline lactone; and on heating with hydrochloric acid, is converted into furfural. The acid plays an important role in the detoxication mechanisms of the body. The animal organism has the capacity to render innocuous the toxic substances by combining them with this acid and thus eliminating them from the system.

It is usually obtained from its derivatives, euxanthic acid or menthol-glucurone by hydrolysis. It is also formed by the reduction of D-saccharo-lactone with Na-amalgam. Its structure is :

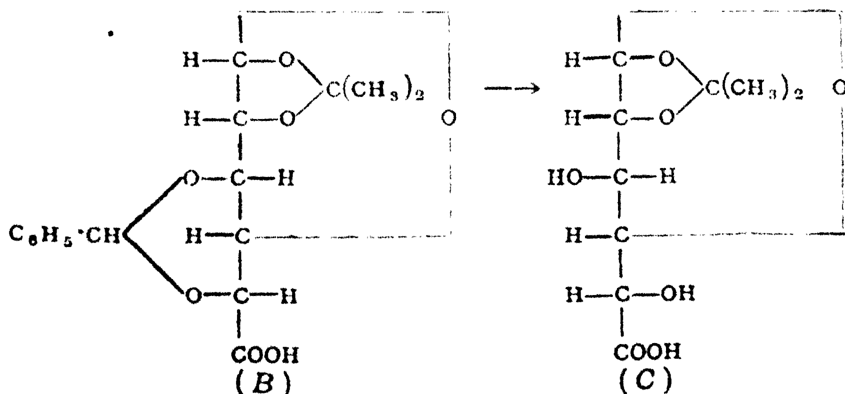


Dglucuronic acid

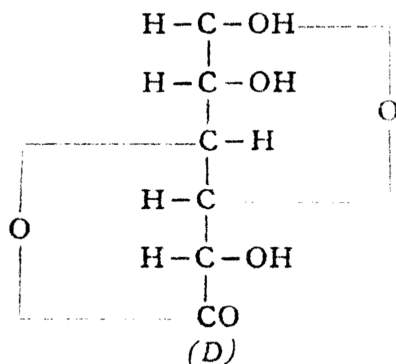
It is obtained from acetone-benzylidene, in which all the hydroxyl groups except the primary are protected. The acetone-benzylidene glucose (*A*) is oxidised to the corresponding acid (*B*) with alkaline potassium permanganate.



The acid (*B*) on catalytic hydrogenation with palladium is converted into acetone glucuronic acid, (*C*). The change involves the elimination of the benzylidene group :—



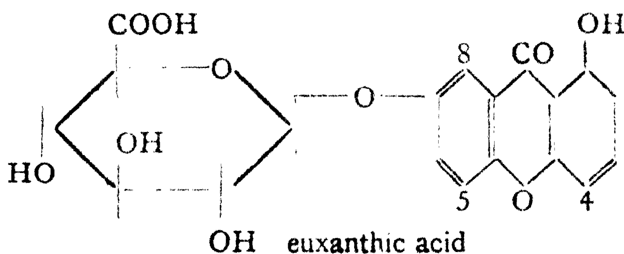
Mild acid hydrolysis of (*C*) removes the isopropylidene group and yields the lactone of glucuronic acid (*D*) :—



(*D*)

The lactone is changed into the sodium salt of the glucuronic acid from which the free acid is obtained on acidifying with a mineral acid.

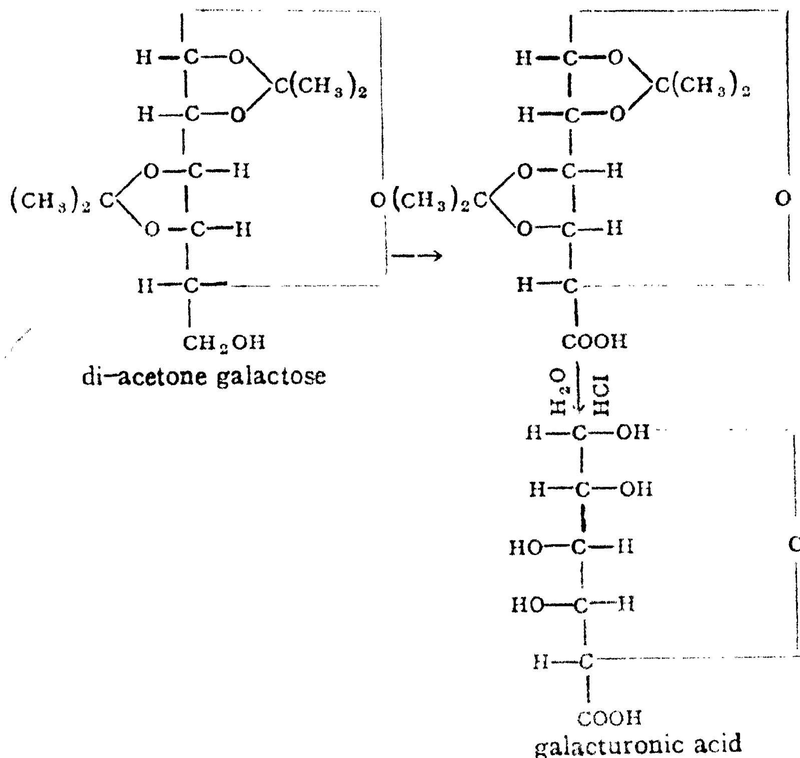
Indian Yellow or Piuri which is used as a yellow pigment is the magnesium salt of euxanthic acid, which is a derivative of glucuronic acid. Cows fed on mango leaves excrete large amounts of the Mg salt which constitutes the chief source of the pigment.



euxanthic acid

D-Galacturonic Acid:—It is found in the fruit pectins. It is also present in the products of hydrolysis of flax-seed mucilage. Niemann and Link have synthesised both the D and L galacturonic acids, starting from 1–2–3–4–di-acetone galactose.

The di-acetone galactose is first oxidised with alkaline $KMnO_4$, to the corresponding acid which, on acid hydrolysis, yields the galacturonic acid.



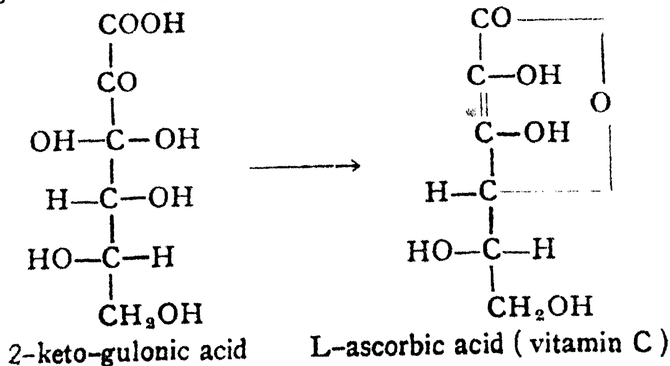
di-acetone galactose

galacturonic acid

D Galacturonic acid exists in two crystalline forms. The presence of the pyranoside ring in the α-isomer has been indicated by the result of hydrolysis.

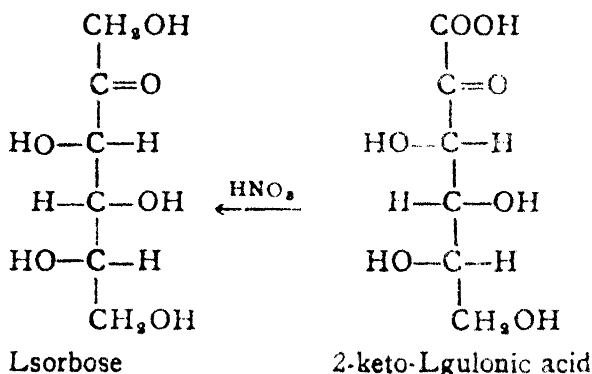
(*iv*) KETO-ACIDS :— Kiliani isolated an oxidation product of glucose which is both an acid and a ketone. The keto group was on C_5. Other keto acids are also known.

Of the keto-acids, the 2-keto-acids possess special significance, because of their relation to vitamin C and related compounds. Thus 2-keto-gulonic acid spontaneously passes into vitamin C.



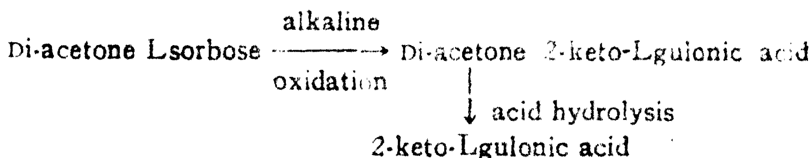
2-keto-gulonic acid L-ascorbic acid (vitamin C)

The 2-keto-acids are obtained from the ketoses by direct oxidation with nitric acid, when a preferential oxidation of the CH_2OH group adjacent to the CO group takes place. Thus, L sorbose gives 2-ketogulonic acid.



Lsorbose 2-keto-Lgulonic acid

Di-acetone derivatives of ketoses have also been used to obtain the 2-keto-acid :—



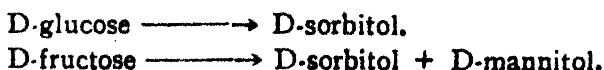
(*v*) KETO-ALDEHYDES (OSONES) :—The di-carbonyl derivatives of sugars obtained by the hydrolysis of the phenylosazones are called osones. Other hexosones have been obtained. On reduction they are converted into the corresponding ketoses.

REDUCTION PRODUCTS OF SUGARS :—A hexose (aldose or ketose) may give rise to different reduction products :—

(*a*) hexa-hydric alcohols or hexitols.

(*b*) desoses. (*i*) 6-desoses (methyl pentoses), (*ii*) 2-desosess (*iii*) 2-6-desoses.

(*a*) HEXA-HYDRIC ALCOHOLS :—On reduction with sodium amalgam, the hexose is converted into a hexa-hydric alcohol ; an aldose gives rise to only one alcohol, while a mixture of epimeric alcohols results from a ketose :—



These alcohols are colourless crystalline compounds; they possess a sweet taste and are soluble in water.

(*b*) (*i*) METHYL PENTOSES OR 6-DESOSES–They represent the hexose reduction products, in which the CH_2OH group is reduced to CH_3. Hence, they are termed 6-desoxy sugars. On boiling with mineral acids they are converted into methyl furfural, while a pentose yields furfural; hence they are called *methyl pentoses*. As they are also directly related to the hexoses. Votoeck has proposed a nomenclature which uses—*methylose* as a general suffix to the hexose. Thus, *L*-rhamnose is called *L*-manno-methylose. The desoxy-sugars show a characteristic test called the Dische test. Thus an intense blue coloration is produced with a desoxy-sugar and diphenylamine, acetic acid and sulphuric acid.

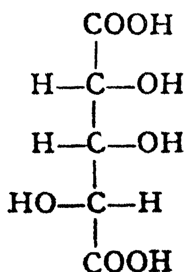
A large number of methyl pentoses is found to occur in nature. The best known is *L*-rhamnose which is present in quercetin from the oak bark. Other methyl pentoses are, *D*-gluco-methylose which is a constituent of convolvulin and *L*-fucose or *L*-galacto-methylose which is the product of acid hydrolysis of some kind of sea-weed.

STRUCTURE OF *L*-RHAMNOSE :—The molecular composition is $C_6H_{12}O_5$. On boiling with acids, it gives methyl furfural. These results indicate that it is a methyl pentose. The presence of hour hydroxyl groups is established by the formation of a tetra-acetyl derivative with acetic anhydride and sodium acetate. It forms an osazone, m. p. 187°. With Br_2 water, rhamnonic acid $C_6H_{12}O_6$ is obtained. Thus, it is an aldo-pentose. Hence, structurally, we can represent it by :—

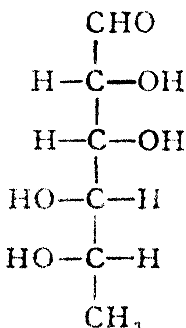


$$CH_3\text{-}(CHOH)_4\text{-}CHO$$

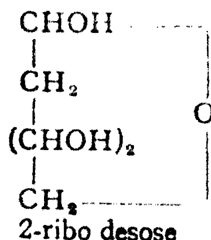
Configuration:—on oxidation with nitric acid rhamnose gives Larabo-trihydroxy-glutaric acid.



This settles the configurations of carbon atoms 2, 3, 4, as a group; (with respect to CHO group) but leaves open whether the α C is positive or negative; also the nature of the C_5 atom is not indicated. These points are settled by the application of the Hudson's rule. Rhamnonic acid gives a lactone which is levorotatory. Hence C_4 must be negative and therefore the ∞ C atom i.e. C_2 must be positive; C_3 must also be positive; further on degradation by the Ruff's method, rhamnonic acid gives methyl tetronic acid; the latter gives a lactone which is levorotatory. Hence C_5 must be $-$ve. Hence the configuration is:



(*ii*) 2-DESOSES :—They are hexoses or pentoses in which the C_2 has been reduced to a methylene group. Ribo-desose has been isolated in a crystalline form from the nucleic acid of thymus Methylation studies have indicated the presence of a pyranoside ring in this desose.



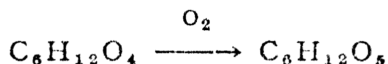
2-ribo desose

The 2-desoses have been synthesised from the glycals. The 2-desoses exhibit great activity.

(*iii*) 2–6 DESOSES :—Kiliani isolated from digitoxin, a glycoside of the digitalis group, a sugar digitoxose which has the molecular composition $C_6H_{12}O_4$ and thus differs from that of a

hexose molecule in having two atoms of oxygen less. The elucidation of its structure based on the following evidence :—

(*a*) With an alkaline hypobromite, a mono-basic acid with the same number of carbon atoms is obtained.



$$C_6H_{12}O_4 \xrightarrow{O_2} C_6H_{12}O_5$$

(*b*) Phenylhydrazine gives readily a phenylhydrazone but no osazone.

These results, therefore, indicate that the sugar contains an aldehyde group but C_2 carries no hydroxyl group; hence, it is probably reduced.

(*c*) Oxidation with silver oxide yields acetic acid as one of the products. This indicates the presence of a terminal methyl group.

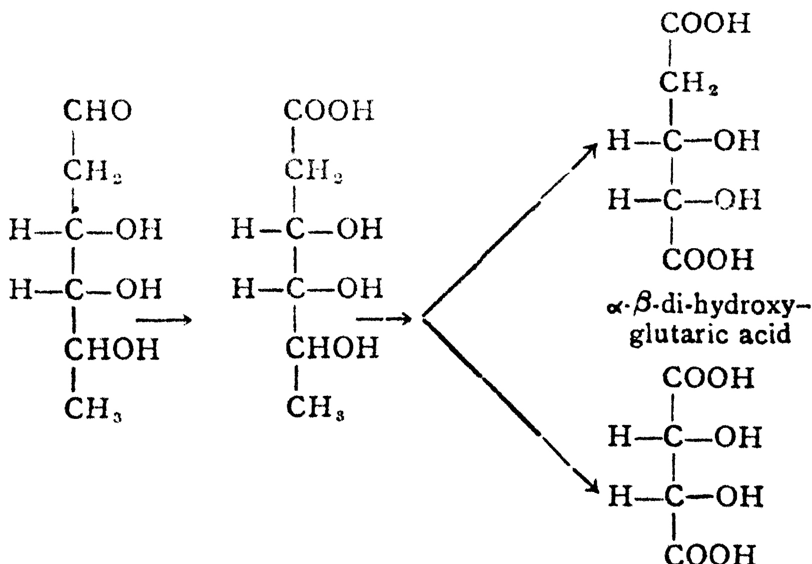
The structure of the sugar digitoxose could, therefore, be represented by :—



$$CH_3—CHOH—CHOH—CHOH—CH_2—CHO.$$

The configuration of the hydroxyl groups attached to C_3 and C_4 was then established from the nature of the products of oxidation with nitric acid. Kiliani found that digitoxose on oxidation with nitric acid gives :—

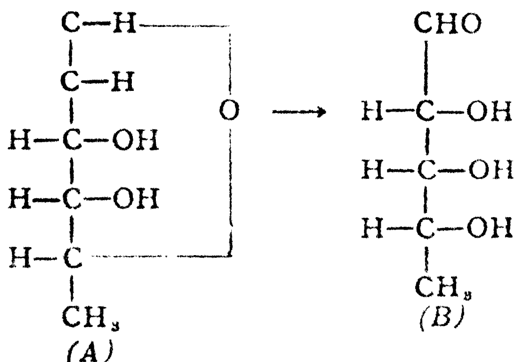
(*i*) α-β-di-hydroxy-glutaric acid, and
(*ii*) meso-tartaric acid.



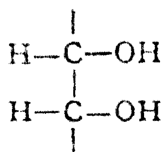
These results, thus, indicate that the hydroxyl groups on C_3 and C_4 are on the same side.

The configuration of the hydroxyl group on C_5 follows from the following further evidence :—

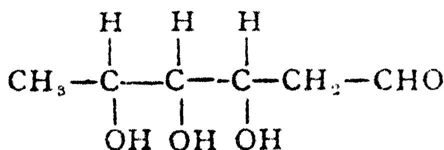
Vacuum distillation of digitoxin gives an anhydro-compound of formula *(A)*, which on ozonisation gives a methyl tetrose *(B)*.



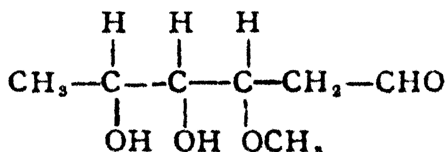
Now the methyl tetrose (*B*) and D arabo-methylose give the same osazone. Hence, the C_4 and C_5 in methyl tetrose and in digitoxose must have the configuration :



But the hydroxy groups on C_3 and C_4 are *cis*; therefore, the complete configuration of digitoxose would be :—



Cymarose, from cymarin, is also a sugar of the digitalis group. It is a methyl ether of digitoxose. The methoxy group is on C_3.

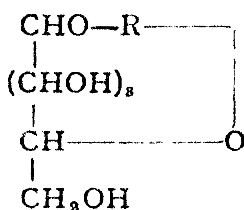


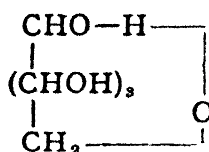
Glycosides

Glycosides are natural products which on acid or enzymatic hydrolsis, yield a sugar molecule and a nonsugar residue or moiety. The latter is called "aglycon"; structurally, the latter may be a hydroxylic compound e.g. alcohol or phenol, or it may be an amine;

Such compounds are related to the α and β methyl glycosides formed from *D* glucose and methanol in presence of HCl gas. Glycoside is a generic term and the specific names. glucosides, mannosides etc. are given to such compounds when they contain glucose, mannose etc. there may be glycosides derived from pentoses.

Thus the general structure of the glycosides is formulated as:





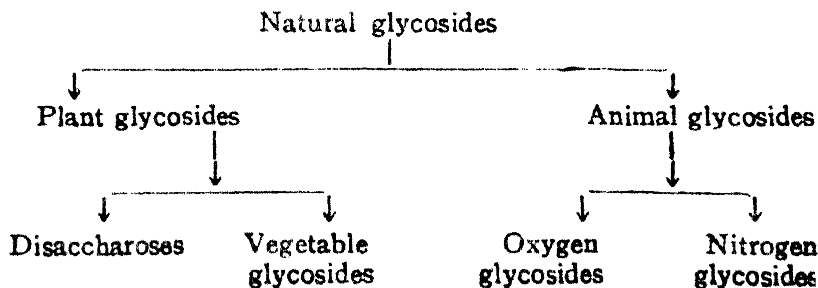
(R = a glycon)

Further, it may be an α or β glycoside corresponding to the α or β menthyl glucosides, depending on its behaviour towards the enzymes. I is derived from a hexose, and II is derived from a pentose. The glycoside derived from the hexoses–are more common, because the hexoses are more abundant as they are the direct products of photosynthesis.

Structurally, they are the acetals of the cyclic forms of the sugars, and as such they are stable to alkali but rapidly attacked by acids.

Classification of the Glycosides:- A more or less scientific classification of the glycosides has been possible : it is based on the mode of their occurrence and the nature of the products of their hydrolysis. Thus we have (*a*) **Synthetic** glycosides *e.g.* α, β, and α methyl glucosides, galactosides etc.; they are not found in nature but are only laboratory products. (*b*) **Natural** glycosides *e. g.* those which occur in nature. They have been further subdivided as :

Natural glycosides



The vegetable glycosides are subdivided further on the basis of the fundamental structure of the aglycon. Thus we have: (*a*) phenolic glycosides. (*b*) hydroxy-flavone glycosides. (*c*) hydroxy coumarin glycosides (*d*) cyanogenetic glycosides (*e*) mustard oil glycosides. etc.

NATURAL VEGETABLE GLYCOSIDES :—The natural glycosides occur in several parts, *e.g.* fruits, barks, leaves etc., of plants and trees. The plant tissue also contains the enzyme that hydrolyses them, but in different cells. It is only on maceration that the tissues are destroyed and the enzyme gets free access to the glycoside and thus effects its hydrolysis.

EXTRACTION OF THE GLYCOSIDES :—The macerated plant tissue is extracted with alcohol or water in a soxhlet; the enzyme present is first destroyed by heating to a temperature of about 65°C. The concentration of the extract gives the glycoside which is then purified by suitable methods. The glycosides are usually insoluble in ether.

GENERAL PROPERTIES—As a class, the glycosides are crystalline compounds and usualls are *l*-rotatory. They are attacked by dilute acids and the enzyme emulsin only. Many of these glycosides possess physiological action and hence find application in medicines and therapeutics.

CONSTITUTION OF NATURAL GLYCOSIDES :—The general procedure for establishing the constitution involves the determination of: (*a*) the nature of the sugar component and of the aglycone; the glycocide is hydrolysed by dilute acids into the sugar and aglycone, which are then identified. (*b*) the nature of the ring' structure in the component sugar; the glycoside is methylated completely by one of the standard methods; the methylated glycoside is then hydrolysed carefully and the configuration and structure of the methylated sugar thus obtained is established by reference to standard methyl sugars.

The pyranose or furanose structure of the component sugar is also established by the periodic oxidation method. The pyranosides yield formic acid on such oxidation, the furanosides give no formic acid at all.

(c) the mode of linking of the sugar residue and the aglycon ; this is established by special methods depending on the nature of the aglycon.

(d) the stereo–chemical form of the glycoside; this is established by the study of the enzyme action *i. e.*, behaviour of the glycoside towards maltase and emulsin. Further the α glycosides possess a high specific rotation and mutarotate downwards, while the β-isomers have a low specific rotation and mutarotate upwards.

Finally, the structure, thus arrived at, by the degradative method is confirmed by a simple and unambiguous synthesis of the glycoside.

The first synthesis of a natural glycoside was achieved by Michael. Aceto-chloro-glucose was condensed with the K-salt of the phenolic compounds. Recently the more reactive aceto-bromo glucose or any aceto bromo-hexose obtained by the action of HBr on the penta-acetate of the hexose in glacial acetic acid is used. The condensation with the aglycone residue is effected in benzene solution in presence of Ag_2CO_3 or quinoline; anhydrous $CaSO_4$ with a little of I_2 is also recommended, the glycoside thus obtained is always the β isomer. However a quantitative yield of the α isomer can be obtained by heating the β isomer with $SnCl_4$ or $TiCl_4$.

Phenolic Glycosides

Salicin : It occurs in the bark and leaves of willow, as also in the flower-buds of meadow-sweet. It is a solid (m. p. 210°) and is *l*-rotatory. It has long been used as an antipyretic and in the treatment of rheumatism. Its therapeutic action depends on the formation of salicylic acid by oxidation of salicyl alcohol present in the glucoside.

Constitution of Salicin : Salicin has the molar composition $C_{13}H_{18}O_7$ and gives the following reactions :—

(a) On acid hydrolysis, it gives *D*-glucose and salicyl alcohol (saligenin) ; hence it is a glucoside of saligenin ; But saligenin which is a solid (m. p. 82°), dissolves in alkali and gives a blue coloration with $FeCl_3$ solution, and contains a *phenolic* as well as a *primary*

alcoholic group through which the glucosidic union may take place. The nature of the OH group involved has been settled thus:

(*b*) Salicin on oxidation with nitric acid gives ***helicin*** the glucoside of salicylic aldehyde;



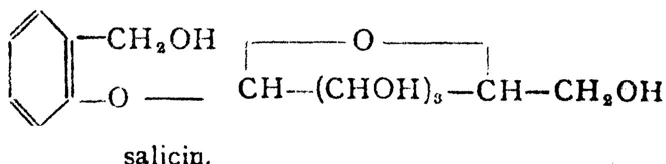
$$C_{13}H_{18}O_7 \xrightarrow{O_2} C_{13}H_{16}C_7 \text{ i. e. } C_{12}H_{15}O_6\cdot CHO$$

salicin helicin

The latter contains a CHO group; hence salicin must carry a free CH_2OH group. The glucosidic union must be therefore through the phenolic OH.

The ring structure of the glucose molecule could not be established by the usual method. Irvine and Rose obtained a penta-methyl derivative of salicin which, however they could not hydrolyse. It is usually found that the methylated natural glycosides show great resistance towards hydrolytic reagents. The problem of the structure was then solved by them by the synthetic method. 2-3-4-6 tetra-methyl glucose and salicylic alcohol were made to interact in benzene solution containing hydrogen chloride to give a syrupy glucoside. The latter, on methylation, gave a penta-methyl derivative identical with the one obtained by the methylation of natural salicin.

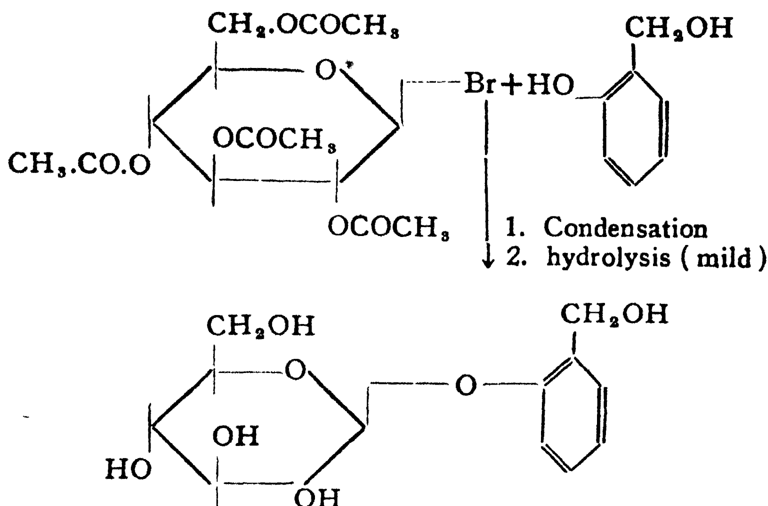
Hence, it follows that the component sugar possesses the pyranoside ring. The structure of the glucoside would, therefore be:—



salicin.

It is hydrolysed by emulsin, hence it represents the β-glucoside. The above structure has been verified by a synthesis. The principle of the method has been discussed already.

Aceto-bromo-glucose is condensed with salicylic alcohol in presence of quinoline or Ag_2CO_3 in benzene. The product formed is then carefully hydrolysed with ammonia as to give salicin.



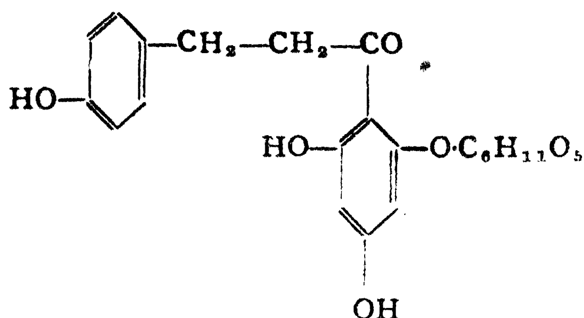
POPULIN :—It is found in the bark of the popular trees; it is the benzoyl derivative of salicin; oxidation of populin with nitric acid gives benzoyl helicin. Hence the benzoyl group must be present in the sugar residue.

ARBUTIN :—It occurs in many plants, specially in the leaves of bear-berry. It is a colourless crystalline compound (m. p. 187°); it possesses a bitter taste and is *l*-rotatory. On hydrolysis, it gives quinol and glucose. Hence, it is the glucoside of quinol; The nature of the ring in the component sugar was established by a study of the products of hydrolysis of methyl arbutin. The latter, on hydrolysis, gives: (*a*) mono-methyl ether of quinol, and (*b*) 2-3-4-6-tetra-methyl glucose. The sugar residue, therefore, must have a pyranose structure; and as it is attacked by emulsin, it is a β-glycoside. Hence the structure of arbutin is

HO—⟨ ⟩—$O{\cdot}C_6H_{11}O_5$. It is synthesised as follows :

Benzoyl quinol was condensed with aceto-bromo-glucose in the presence of Ag_2O and quinoline, and the benzoyl arbutin thus obtained was treated with ammonia to give arbutin.

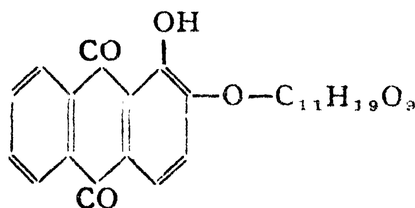
Phloridizin, found in the bark of plum and apple trees is the glucoside of phloretin and has the structure :



GAULTHERIN is the glycoside of methyl salicylate. On enzymatic hydrolysis, it gives methyl salicylate, glucose and xylose. The sugar residue is thus the primeverose molecule.

HYDROXY-ANTHRAQUINONE GLYCOSIDES

The most important glycoside belonging to this class is ruberythric acid, found in the madder root. The latter was one time, the source of commercial alizarin. Ruberythric acid, on hydrolysis gives alizarin, glucose and xylose. The two sugars are present as the disaccharose, primeverose.



Ruberythric acid

Other anthraquinone glycosides are *chrysophanin* found in rhubarb and aloes, and *frangulin* found in chines rhubarb. They find application as purgative, The former is the glucoside of chrysophanic acid and the latter is a rhamnoside of frangulaemodin.

HYDROXY-COUMARIN GLYCOSIDES

Aesculin found in the bark and buds of the horse-chestnut tree is important member of this class. It is used as a protection against sunburn. Structurally it is (6, 7-dihydroxycoumarin) 6-β-glucopyranoside.

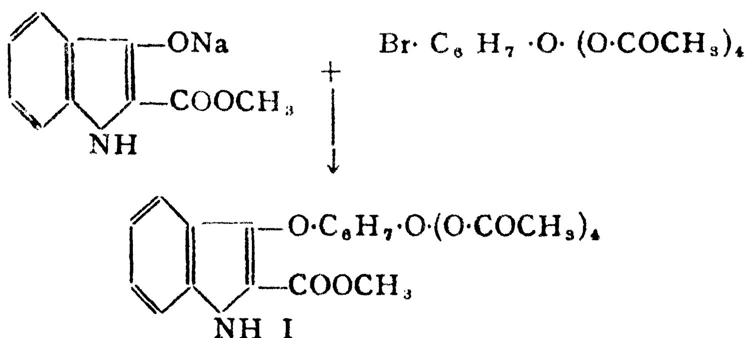
Hydroxy-flavone glycoside, the yellow and brown colouring matters of plants are the glycosides of the hydroxy-flavones. Similarly the closely related, blue and red pigments of flowers and

fruits are the glycosides of the hydroxy-flavylium system. Both these colouring matters are discussed in some detail elsewhere.

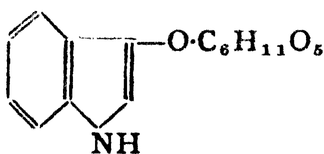
INDOXYL GLYCOSIDE

Indican is a crystalline compound with the molecular composition $C_{14}H_{17}O_6N \cdot 3\ H_2O$. On hydrolysis, it gives glucose and indoxyl. These results indicate that it is the glucoside of the aglycone, indoxyl. The nature of the sugar is revealed by the formation of 2, 3, 4, 6 tetra-methyl glucose on hydrolysis of methyl indican. The latter was hydrolysed by methanol containing 1% HCl. This type of hydrolysis overcomes the usual resistance displayed by the methylated natural glycosides. Thus, indican is indoxyl-3. β-pyranoside. It is hydrolysed by indimulsin and is therefore a β-glycoside.

This structure is further confirmed by a synthesis : the sodium derivative of the enolic form of methyl ester of indoxylic acid is condensed with aceto-bromo glucose in acetone, in presence of KOH,



I is then treated with KOH in CH_3OH and the K-salt obtained is fused with Na-acetate and acetic anhydride give l-acetyl-3-O-tetra-acetyl-β-glucosido-indole; the latter on mild hydrolysis with ammonia gives a product identical with the natural product.



indican.

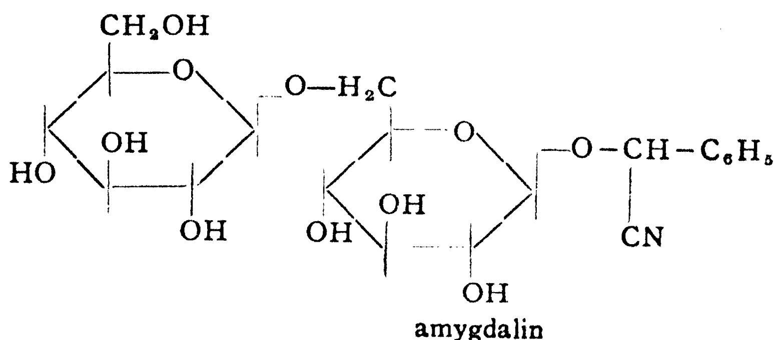
Amygdalin is the important glycoside belonging to this class. It is a crystalline compound, which is hydrolysed by emulsin as follows :—



$$C_{20}H_{27}O_{11}N + 2H_2O \longrightarrow C_6H_5CHO + HCN + 2C_6H_{12}O_6$$

amygdalin

By the action of yeast extract, however, a new glucoside, mandelonitrile glucoside together with a molecule of glucose, is obtained. As only one hydroxyl group is available, a disaccharose must be present in amygdalin ; further it was shown by Haworth to be the rare gentiobiose. The latter is a reducing sugar and the products of hydrolysis of the methyl-gentiobiose are 2, 3, 4, 6-tetramethyl glucose and 2, 3, 4 trimethyl glucose, which establish its structure as a C_6 disaccharose. Hence amygdalin has been assigned the structure :



amygdalin

It is a β-glucoside. The above structure has been confirmed by a synthesis, which starts from acetobromo-gentiobiose and ethyl *dl*-mandelate.

Mustard Oil Glycosides

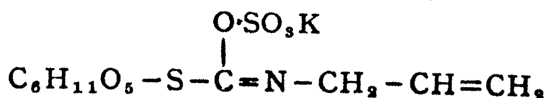
The black mustard seed contains the glycoside, *sinigrin*, the simple member of this class. It is hydrolysed by the enzyme, myosin, specific for this class of glycosides.



$$C_{10}H_{16}O_9NS_2K \rightarrow C_6H_{12}O_6 + KHSO_4 + CH_2{=}CH-CH_2-N{=}C{=}S$$

sinigrin allyl-iso-thio-cyanate

By the action of Na or K-methoxide sinigrin yields thio-glucose $C_6H_{11}O_5 \cdot SH$, whence Gadamer has proposed the following

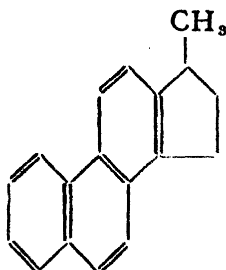


$$C_6H_{11}O_5-S-\underset{}{\overset{O\cdot SO_3K}{\overset{|}{C}}}{=}N-CH_2-CH{=}CH_2$$

structure for the glycoside. It is not known whether it is an α or β glucoside.

Saponins

The saponins form a group of closely related glycosides widely distributed in nature. Their aqueous solutions froth like soap solution when shaken. They are very toxic to cold blooded animals such as fish. In red blooded animals also, they cause hæmolysis. On acid hydrolysis, a saponin yields sugar molecules and the aglycone called sapogenin. The saponin from sarsaparilla root, sarsaponin gives on hydrolysis, glucose, rhamnonse and sarsasaponin. The latter has been shown to contain the cyclopenteno-phenanthrene system—the system present in the steroids and the steroidal hormones, because on dehydrogenation with selenium, methyl-cyclo-pentenphenanthrene is formed.



The saponins, *digitonin*, and gitonin also belong to this group. The glycosides isolated from Digitalis and strphanthus spp. used in medicine for stimulation of the heart muscle, are related to the steroids. The sugar residues in these glycosides are however, the desoxy sugars.

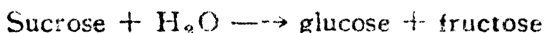
Nitrogen Glycosides

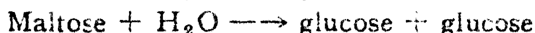
The nucleic acids, in which the union to the aglycone is made through N, belong to this class of glycosides. The nucleic acids are built up of nucleotide units and the latter are the nitrogen glycosides of pyrimidines or purines, which are esterified on the sugar residue with phosphoric acid; usually, the sugar present is *D*-ribose or 2 desoxy-*D*-ribose. The pyrimidines involved are cytosine and uracil, and the purines such as adenine and guanine. The nucleotides, on heating with water or mild alkali, lose H_3PO_4 and yield *nucleosides*. The latter are the glycosides of the aglycones such as pyrimidines or the purines.

Disaccharoses

The glycosides which contain a sugar residue *i. e.* R = a sugar residue, in the general formula are called disaccharoses. They are thus glycosides of mono-saccharoses themselves. The mono-saccharose may be a hexose or a pentose; it may be an aldose or a ketose. The most commonly occuring disaccharoses are dihexoses built up of hexoses; glucose, fructose, galactose and mannose. Less common are the disaccharoses; vicianose and primeverose, with molar composition $C_{11}H_{20}O_{10}$. Vicianose on hydrolysis gives glucose and arabinose. *Primeverose* is a xylosido-glucose which on hydrolysis gives glucose and xylose. It is found to be present in ruberytbric acid. Disaccharoses are also obtained by hydrolysis of polyoses. Cellobiose is thus obtained by careful hydrolysis of cellulose, while enzymic hydrolysis of starch gives maltose.

The most common disaccharoses, are the crystalline. sweet compounds of known molecular weight. They are soluble in water and are usually *l*-rotatory but sucrose is *d*-rotatory. They possess the molecular composition $C_{12}H_{22}O_{11}$. and on hydrolysis by acids or enzymes, give two molecules of hexoses; the two molecules may be of the same hexose or different hexoses. The more commonly known natural disaccharoses are sucrose, maltose, lactose. The products of hydrolysis of these disaccharoses are :


Sucrose + H_2O ⟶ glucose + fructose


Maltose + H_2O ⟶ glucose + glucose


Lactose + H_2O ⟶ glucose + galactose

Classification of Disaccharoses :—The disaccharoses are classified as (*i*) *reducing* and (*ii*) *non-reducing*. The reducing disaccharoses give the characteristic reactions of a free or potential carbonyl group: they (*a*) reduce Fehling's solution, (*b*) form well-defined crystalline osazones with excess of phenylhydrazine, (*c*) on mild oxidation with bromine water, give monobasic acids, bionic acids, of the molecular composition $C_{12}H_{22}O_{12}$: and (*d*) show mutarotation. The non-reducing sugars do not show these characteristics. A more recent classification is based on the nature of the glycosidic combination present in the disaccharose. According to this division we have :—

(*a*) those linked through the glycosidic C_1 *i.e.* C_1 disaccharose ; these correspond to the *non-reducing* type.

(*b*) those linked through C_4 *i.e.* C_4 disaccharoses, and

(c) those linked through C_6 *i.e.* C_6 disaccharoses.

The sugars belonging to (b) and (c) are the *reducing*: sugars which carry a free or potential carbonyl group.

THE STRUCTURE OF THE DISACCHAROSES

The determination of structure of a disaccharose involves the elucidation of :—

(1) the nature of the component sugars,

(2) the nature of the ring *i.e.* pyranose or furanose structure of the component sugars.

(3) which of the Component sugars function as the alcoholic component.

(4) the location of the carbon atoms involved in the glycosidic combination. As they are glycosides they possess the general formula referred to above and hence we have to decide which of the carbon atoms of the alcoholic sugar component is involved in the glycosidic union with aldehydo-hydroxyl (*i.e.* glucosidyl) of the glucose molecule. The nature of the glycosidic union is established by the method of methylation, oxidation etc.

(5) the stereo-chemical nature, α or β, of the glycosidic union. (*a*) when both the glycosidic OH groups are involved, we have the stereochemical combination:—(*i*) α and α, (*ii*) α and β, (*iii*) β and β; these will represent the non-reducing sugars. (b) when only one glycosidic OH group is involved, the stereochemical combinations may be (*i*) α or (*ii*) β and the free glycosidic group may exist in α or β forms. These will represent the *reducing* sugars. This is determined by enzymic studies and by a consideration of the optical rotation values of the glycosides. An α-glycoside is attacked by maltase, while emulsin attacks only the β one. The α-glycosides have very high specific rotations and the β ones have low ones. The above procedures will now be discussed in some detail.

THE NATURE OF THE COMPONENT SUGARS :—The disaccharose is hydrolysed by acid or enzymes and the component sugars separated and identified by the osazone method.

THE NATURE OF THE RING SYSTEM AND THE LOCATION OF CARBON ATOMS INVOLVED IN THE GLYCOSIDIC COMBINATION :- The free unsubstituted sugar itself cannot be used in these investiga-

tions. During the hydrolytic degradation or any other degradation method employed. the molecule of the sugar may undergo structural alterations. Methylation was found to be the most reliable and practical method of preventing such alterations. The methylation of the disaccharoses is carried out by Haworth's method. The normal procedure adopted involves:

(*a*) the preparation of a methylated disaccharose. It is also easier to manipulate with methyl sugars, as they are more stable and more soluble in organic solvents. They can thus be readily separated and identified.

(*b*) the carefully controlled hydrolysis of the methylated disaccharose into a mixture of methylated monosaccharoses.

(*c*) the separation and identification of the structures of each of these methyl hexoses.

(*d*) the location of the carbon atoms involved in the glycosidic union.

During the hydrolysis of the methylated disaccharose one fresh hydroxyl group is introduced into each of the hexose units, at the points which were involved in the glycosidic combination. The location of the free *OH* groups, in the methylated hydrolytic products, decides the nature of the glucosidic union. The hydroxyl groups which were present as such in the free sugar and which had not taken part in the glucosidic formation, appear as methoxy groups in the fission products.

A number of methylated and partly methylated hexoses have been carefully synthesised and their structures established by the Zeisel determination and oxidation reactions. These, then, are used as the standard or reference compounds, and the structure of fission products established by reference to these standards. This method was successfully developed by Irvine. Some of the important methylated sugars used as such standards are :—

2-3-4-6-*tetra-methyl glucose* ;—It was obtained from α and β methyl glucoside by methylation and subsequent hydrolysis.

1-3-4-5-*tetra-methyl fructose* :—First obtained by Purdie and Paul as crystalline compound. Irvine and Patterson reported its preparation from β-methyl fructoside of Hudson and Brauns. The

pyranose structure for this derivative was established by Haworth and Hirst by the usual oxidation technique.

2-3-4-6-tetra-methyl galactose :—It was obtained as a syrup by Irvine and Cameron. The pyranose ring was demonstrated by the oxidation method (Haworth and Jones).

2-3-6-tri-methyl glucose :—This was obtained as a product of hydrolysis of methylated cellulose by Denham and Woodhouse. Haworth and Hirst converted it into *2-3-4-6-tetra-methyl glucose.* This is a product of partial methylation of methyl glucoside (Purdie and Irvine). The above structure is based on the experimental work of Irvine and Oldham, Charlton and Haworth.

A number of methods have been devised and improved for the preparation of partly methylated sugars. The fundamental principle underlying these methods is that a group or groups capable of subsequent removal by hydrolysis *e. g.* acyl group, isopropylidene, benzylidene or carbonato groups, are introduced into sugar molecule, and the remaining hydroxyl groups are them methylated. These products, on hydrolysis, yield partly methylated sugars. The constitution of these derivatives is established by the usual methods.

THE STEREO-CHEMICAL NATURE OF THE GLUCOSIDIC UNION : This problem is readily solved by the study of the behaviour of the disaccharose towards a particular enzyme. The action of the enzyme is highly specific. The enzyme *emulsin* attacks the β glucosides only, while the α-isomer is hydrolysed by maltase. All the natural disaccharoses are attacked by emulsin and are therefore β glucosides. Studies of the optical rotation of the disaccharoses can also be used to determine the stereo-chemical nature.

Zemplen has devised a method for the determination of the type of the disaccharose. It is applicable to reducing sugars only. It is based on the determination of the extent of degradation of the disaccharose that would be necessary before the truncated disaccharide no longer formed an osazone.

Recently the method of Hudson and Jackson has been used. With periodic acid the different types of disaccharoses (eg. C_2, C_4, C_6) behave differently. The C_4 disaccharoses liberate I_2 while C_6 disaccharoses do not, on oxidation with periodic acid.

GENERAL METHODS OF SYNTHESIS OF DISACCHAROSES :-One of the most important general methods of synthesis of a disaccharose involves the use of aceto-bromo-glucose. The latter is condensed with another acetylated sugar molecule to give an acetylated disaccharose. The condensation is carried out in an inert solvent like chloroform or benzene in presence of Ag_2CO_3 or quinoline. The acetyl groups are then removed by carefully controlled hydrolysis to obtain the free disaccharose. The acetate is allowed to stand with $Ba(OH)_2$ for 24 hours at the room temperature. The $Ba(OH)_2$ is subsequently removed by passing in CO_2 into the solution. Sometimes NH_4OH at O° is used to hydrolyse the acetyl groups.

In another method, the two component sugars are heated together for some time. The product is acetylated and the acetyl derivative separated by chromatography and finally hydrolysed.

The action of an enzyme is the basis of another method of synthesis. As the action of the enzyme is reversible, the enzyme which attacks a natural disaccharose has been used to synthesise the same dissccharose. Thus, the syntheses of maltose from β-glucose, and of lactose from a mixture of β-glucose and β-galactose, have been achieved of Pictet and his collaborators. These enzymic syntheses; however, give no indication as to the struture of the disaccharose formed. On the other hand the syntheses involving the use of aceto-bromo-glucose are more definite as regards the structure of the disaccharoses synthesised.

The constitutions of some typical disaccharoses will now be discussed :—

SUCROSE :—It is widely distributed in nature, the chief sources being the sugar-cane and the beet. Large quantities of it are manufactured and used for sweetening purposes.

Its constitution is based on the following evidence :—

(*i*) The mohar composition of sucrose is $C_{12}H_{22}O_{11}$.

(*ii*) On acetylation by the usual procedure, sucrose gives an octa-acetyl derivative. This shows that sucrose carries *eight* hydroxyl groups.

(*iii*) On acid hydrolysis or by the action of enzyme invertase, sucrose is split up into an equimolar mixture of glucose and fructose.

called the "invert sugar." Hence sucrose is built up of the two hexose units.

$$\left[\begin{array}{l} K \text{ for cane sugar is } + 66\text{-}5 \\ \quad \text{for invert sugar is} - 20\text{-}0 \end{array}\right]$$

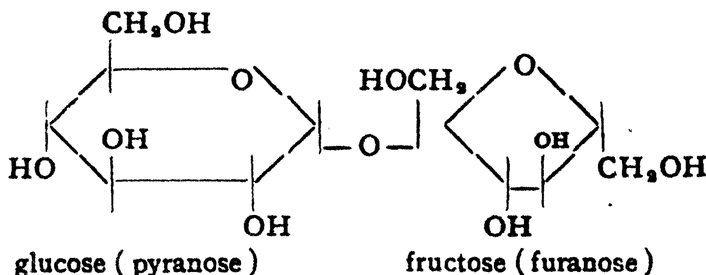
(*iv*) Sucrose does not reduce Fehling's solution or ammoniacal silver nitrate solution. Hence, the sugar molecule carries no free or potential carbonyl group and the glycosidic union must have taken place through the glucosidic C atoms of both the hexose units.

It is hydrolysed much faster than maltose or any other reducing disaccharide. This indicates that the C_1 linkages are more rapidly attacked.

On complete methylation, an octa-methyl derivative is obtained. Haworth and Law subjected this octa methyl derivative to carefully controlled hydrolysis. There was no inversion. The specific rotation of the mixture is + 56·57. From the reaction mixture, they isolated a crystalline tetra-methyl glucose and *d*-rotatory tetra-methyl fructose by high vacuum distillation. The latter, however was not identical with the standard 1-3-4·5 tetra-methyl fructose (Purdie and Irvine). Hence, the fructose component of the sugar must contain a different ring structure.

But there was some practical difficulty of separating the mixture of two isomeric tetra-methyl hexoses. Hence Haworth started with hepta-methyl sucrose, which was readily obtainable and subjected it to careful hydrolysis. He could isolate from the hydrolysis product the same syrupy and *d*-rotatory tetra-methyl fructose and a trimethyl glucose. The former was subsequently identified as the 1-3-4-6 tetra-methyl fructose. On oxidation it gave dimethoxy succinic acid characterised by its crystalline amide. The tri-methyl glucose, on methylation gave the normal 2-3-4-6 tetra-methyl glucose.

The above results show that sucrose is built up of glucose and fructose units. The glucose unit has the pyranose structure and the fructose unit possesses the furanose ring. Further, as it is a non-reducing sugar, the two glucosidic carbon atoms, one of each of the units, are involved in the glycosidic union. therefore, sucrose may be best represented by:—



glucose (pyranose)   fructose (furanose)

Sucrose is thus a C_1 disaccharose which is *non-reducing.* It is both a glucoside and a fructoside.

This structure readily explains the observed non-inversion of the completely methylated sucrose. Both the methylated hexose units contain the ring formed by the hydroxyl groups lying to the right and hence, they are both dextro-rotatory (Hudson's lactone rule). However, when the free unmethylated sucrose is hydrolysed the labile γ-fructose which is first formed, spontaneously changes into the stable normal pyranose structure, and hence, the inversion. Sucrose is an α, glucoside, as indicated by its behaviour towards maltase; but it is attacked by taka–invertase which is a specific enzyme for β fructosides. Hence sucrose has the α–β linkage It is α glucoside and β fructoside.

CONFIRMATION BY SYNTHESIS :—Pictet and Vogel isolated a crystalline tetra-acetyl derivative of fructose with a dextrorotatory power. It was condensed in chloroform solution with tetra acetyl glucose in the presence of phosphorus pentoxide. A crystalline octa-acetyl sucrose was obtained, which on careful hydrolysis gave sucrose. The synthesis however, does not establish the stereochemical nature (α or β) of the carbon atoms involved in the glycosidic combination. The evidence, so far obtained, indicates that α-hydroxyl group of the glucose molecule is linked with the β-hydroxyl group of the fructose molecule. However, it is not quite conclusive. The reported synthesis has not been subsequently confirmed.

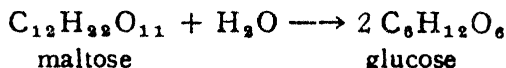
Recently, Hassid has reported that a synthesis of sucrose has been effected by the action of an enzyme phosphorylase, on a mixture of glucose-phosphate and fructose.

Lemieux and Huber have announced a chemical synthesis of sucrose. A mixture of 1. 2, glucose anhydride 3, 4, 6 triacetate and

1, 3, 4, 6 tetra acetyl fructose, is heated at 100° for several days. (The fructose derivative is obtained by the action of HBr in glacial acetic acid on the triacetate of fructose produced by the acetolysis of insulin). Deacetylation, chromatography and reacetylation gives sucrose octa-acetate.

MALTOSE :—Starch on hydrolysis with the enzyme diastase gives along with the dextrins, a disaccharose, maltose. It has the molar composition $C_{12}H_{22}O_{11}$, and gives the following reactions ;—

(*a*) On acid hydrolysis, it gives two molecules of glucose only.



$$\underset{\text{maltose}}{C_{12}H_{22}O_{11}} + H_2O \longrightarrow \underset{\text{glucose}}{2\,C_6H_{12}O_6}$$

It is thus built up two glucose units.

(*b*) It readily reduces Fehling's solution and forms an osazone. It should, therefore, carry a free or potential carbonyl group.

(*c*) On oxidation with bromine water, maltose gives a mono-basic acid, malto-bionic acid, $C_{12}H_{22}O_{12}$. These results confirm that it is a reducing sugar.

(*d*) On acetylation, two isomeric octa-acetyl derivatives are formed; this shows the presence of eight *OH* groups in the molecule.

(*e*) On complete methylation, an octa-methyl derivative was obtained by Perdie and Irvine. On mild hydrolysis, this octa-methyl derivative gives a hepta-methyl derivative. Haworth and Leitch have confirmed the methylation results of Purdie and Irvine. Further from the hydrolysis of the hepta-methyl maltose, they isolated two products : (*a*) 2-3-4-6-tetra-methyl glucose and (*b*) 2-3-6-tri-methyl glucose.

It is thus, obvious that there are present in the molecule, two different types of units : (*i*) *reducing* and (*ii*) ***non-reducing***. The reducing residue loses one methoxy group on acid hydrolysis because it carries the glycosidic hydroxyl group. Hence, the tetra-methyl glucose is derived from the non-reducing unit, and the tri-methyl glucose from the reducing unit, and as the 2-3-4-6-tetra-methyl glucose is obtained from the non-reducing part of the molecule, this unit must possess the pyranose structure.

NATURE OF THE GLYCOSIDIC UNION :—As 2-3-6-tri-methyl glucose is formed, C_1,C_4 and C_5 are free and hence, the reducing

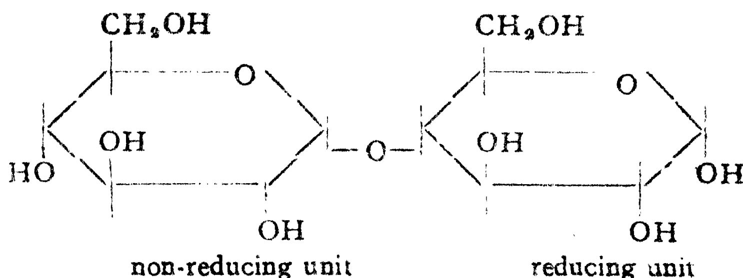
unit may have the pyranose or furanose structure. Further it is obvious that one of the two positions—4 or 5—must be involved in the glycosidic union of the two units. Haworth and Peat definitely located the glycosidic union, on C_4. Maltose was oxidised to maltobionic acid and its calcium salt was completely methylated to form methyl-octa-methyl malto-bionate (8 methoxy groups and one methyl ester $COOCH_3$ group). In the oxidation of maltose to the acid, the oxide ring in the reducing unit would be opened up and a fresh hydroxyl group generated on the carbon atom involved in the oxide ring formation. On subsequent methylation, this *OH* group suffers methylation. Hence, in the methylated malto-bionic acid, the reducing unit has lost its oxide ring but contains a new methoxy group on the carbon atom involved in the ring formation. On hydrolysis, the octamethyl malto-bionate gives: (*a*) 2-3-4-6-tetra-methyl glucose, and (*b*) 2-3-5-6-tetra-methyl gluconic acid. The latter comes from the reducing unit. But when hepta-methyl maltose is hydrolysed we get: (*a*) 2-3-4-6-tetra-methyl glucose, and (*b*) 2-3-6-tetra-methyl glucose. The extra methyl group which appears in C_5 position is obviously due to the opening up of the lactol ring with consequent generation of a new *OH* group (which later on suffers methylation. Hence the reducing, sugar, contains 1 : 5 or the pyranose ring ; and therefore, the glycosidic linkage must be on C_4.

The same conclusion may be reached as follows:—The formation of 2–3–5–6–tetra–methyl gluconic acid which readily forms a stable lactone points to a free hydroxyl group in position 4. This must have been generated only during the hydrolysis of the glycosidic combination. The glycosidic union must therefore, have been formed through this position *i. e.* 4. This leaves the position 5 for the lactol ring in the reducing unit.

Recently, Zemplen has established the position of the glycosidic ring by a new technique. It is based on the determination of the extent to which degradation of the sugar, has to proceed, before the truncated sugar molecule can no longer form an osazone. Maltose oxime was degraded by the Wohl's method (with the new modification) first to α-glucosido-*D*-arabinose, which by repetition of the process, was changed into α-glucosido-*D*-erythrose. The degradation could not be continued further and the new disaccharose

would not form an osazone. Hence it followed that the next hydroxyl group was involved in the glycosidic union, which must be the C_4 in the maltose molecule.

Hence, the constitution of maltose may be written as —



Maltose is a typical C_3 disaccharose. It is attacked by maltase only. Hence it is an α-glycoside.

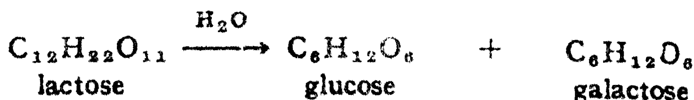
Maltose octa-acetate has been obtained by heating a mixture of equal amount of $\alpha+\beta$ Dglucoses at 160° and acetylating the product. Maltose is synthesised by the action of yeast on D-glucose.

CELLOBIOSE :—This is obtained from cellulose; the latter is subjected to acetolysis with a mixture of acetic anhydride and sulphuric acid, when cellobiose-octa-acetate is formed; on deacetylation, with $NaOCH_3$ in chloroform solution, cellobiose is produced.

It has the molar composition $C_{12}H_{22}O_{11}$. It is hydrolysed by emulsin to give two molecules of glucose. The rest of the evidence for the constitution is the same as for maltose. Hence it is structurally identical with maltose, but differs in the stereochemical configuration. It is a β glucoside, while maltose is an α-glucoside.

LACTOSE :—This is the sugar of milk and is present in the milk of all mammals. Commercially it is obtained from the cow's milk. Its molecular composition is $C_{12}H_{22}O_{11}$. Its constitution is based on the following experimental evidence.

(a) One hydrolysis, with dilute acids it gives a mixture of glucose and galactose.



$$\underset{\text{lactose}}{C_{12}H_{22}O_{11}} \xrightarrow{H_2O} \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{galactose}}{C_6H_{12}O_6}$$

It is thus built up of a galactose and glucose molecules.

(*b*) It readily reduces Fehling's solution and forms an osazone. The sugar, therefore, is a reducing sugar.

(*c*) On oxidation with bromine water, lacto-bionic acid $C_{12}H_{22}O_{12}$ is formed which, on hydrolysis, gives: (*i*) *D*-gluconic acid and (*ii*) *D*-galactose. The glucose residue must, thus, possess the reducing group. This is further confirmed by the results of the hydrolysis of lactosone into glucosone and galactose. Hence lactose is a galactoside.

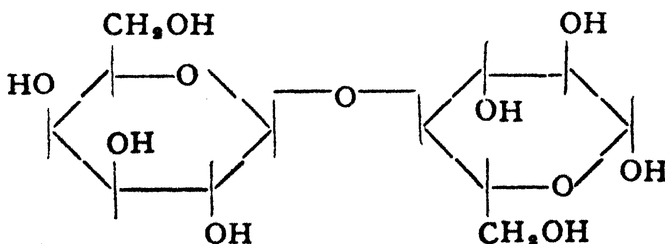
(*d*) The crystalline methyl-hepta-methyl lactoside was obtained by complete methylation of lactose. On hydrolysis, it gave:

(*e*) 2-3-4-6 tetra-methyl galactose, and (*ii*) 2-3-6-tri-methyl glucose. These results show that galactose is the non-reducing unit in the lactose molecule and further that either C_4 or C_5 in the glucose residue must be linked in the glycosidic combination.

(*f*) The hydrolysis of methyl-octa-methy lacto-bionic acid yields: (*i*) 2-3-4-6-tetra-methyl galactose and (*ii*) 2-3-5-6: tetra-methyl gluconic acid. Hence C_5 which carries a methoxy group in the lacto-bionic acid and which is blocked in the disaccharose, must have been involved in the lactol ring formation. Therefore, C_4 which has escaped methylation as is indicated by the formation of 2-3-6-tri-methyl glucose must have taken part in the glycosidic combination. Hence, lactose must be a C_4 disaccharide.

It is not attacked by maltase but is readily hydrolysed by the enzyme lactase. Recently, Helferich has proved the identity of lactase with emulsin. Lactose, thus, is a β-*glycoside*.

Therefore we have: lactose is a C_4 disaccharide and it is a β galactoside; its constitution is



GENTIOBIOSE :—This was first isolated by Bourquelot and Herissey from the gentain root. It is also the disaccharose of the natural glycoside, amygdalin, of bitter almonds. It has the composition $C_{12}H_{22}O_{11}$. The proof of its constitution is based on the following reactions :—

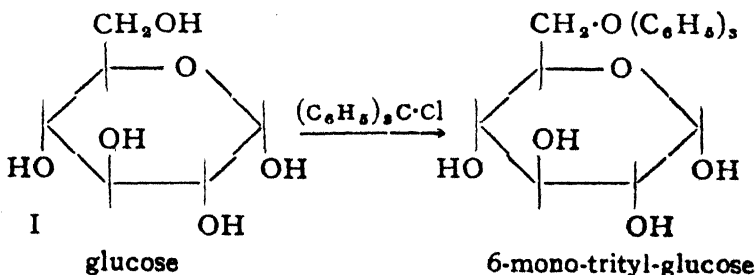
(*a*) On acid hydrolysis, it gives two molecules of glucose. It is therefore, built up of glucose units.

(*b*) It is attacked by emulsin ; hence it is a β-glucoside.

(*c*) It reduces Fehling's solution and forms an osazone. Therefore it is a reducing sugar.

(*d*) Haworth and Wylam completely methylated gentiobiose and obtained a crystalline methyl-hepta-methyl gentiobioside. The latter, on hydrolysis, gives: (*a*) 2-3-4-6-tetra-methyl glucose, and (*b*) 2-3-4-trimethyl glucose.

This indicated that the lactol ring is on C_5 and the glycosidic union on C_6 or *vice versa*. The exact nature of the glycosidic union was proved by a synthesis by Helferich and his collaborators. The different steps in the synthesis are :— Glucose (I) is treated with triphenyl methyl-chloride $(C_6H_5)_3$ C·Cl (also called trityl-chloride) to form the corresponding 6-mono-trityl ether (II)

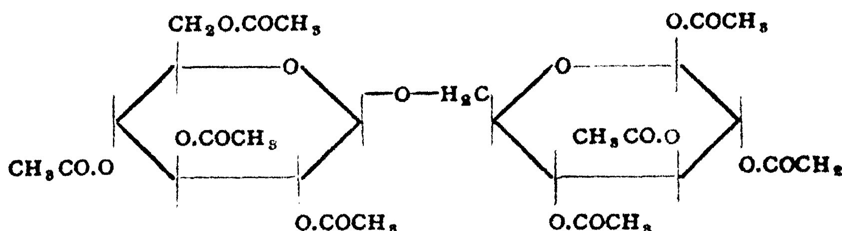


glucose 6-mono-trityl-glucose

The location of the trityl-group is established by its conversion into 6 bromo-glucose by treatment with phosphorus pentabromide.

The remaining hydroxyl groups are then acetylated with acetic anhydride and the trityl-group removed by mild hydrolysis with hydrogen bromide, leading to the formation of, 1, 2, 3, 4, tetra-acetyl glucose.

The above compound has only the sixth position free which is then condensed with aceto-bromo-glucose in presence of Ag_2CO_3 in chloroform to yield the following compound, which would be a C_6 disaccharose derivative.

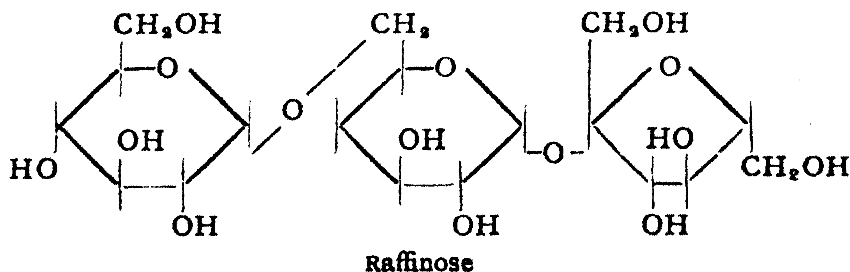


The above compound is identical with gentio-octa-acetate, obtained by the acetylation of the natural gentiobiose. Hence gentiobiose is a C_6disaccharose.

MELIBIOSE : This is obtained from raffinose, by the partial hydrolysis with the enzyme invertase. On acid hydrolysis, melibiose is converted into a mixture of glucose and galactose. It has been shown, by the standard methods, to be 6-D-glucosido-α-D-galacto-pyranoside.

TRISACCHAROSES

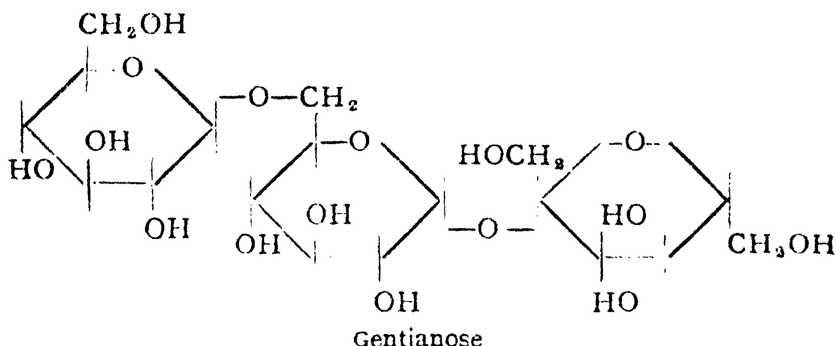
Raffinose and gentianose, are the two common non-reducing natural trisaccharides. Raffinose is the most abundant triaccharide and occurs in beet and in manna—found on eucalyptus trees. Raffinose, on acid hydrolysis, gives equimolar proportions of three sugars glucose, fructose, and galactose. Invertase converts it into a mixture of fructose and melibiose, while α galactosidase which specifically attacks an α-galactosido-linkage degrades it into sucrose and galactose. Hence it follows that in raffinose, galactose and glucose are linked up as in melibiose, and fructose is linked on to the glucose residue as in sucrose.



Raffinose

The above structure is confirmed further, by methylation studies.

GENTIANOSE :—This is present in the gentian roots. On complete acid hydrolysis, one molecule of this trisaccharide gives two molecules of glucose and one of fructose. However with 2% H_2SO_4 or with invertase, gentiobiose and fructose are formed : still with another enzyme, β-glucosidase, specific for the β-glucosidic linkage, the products of degradation are sucrose and glucose. Hence it must be rerpesented by β fructo-furanosidyl-α-gentiobioside.



Gentianose

POLYOSES : STARCHES AND CELLULOSES

OCCURRENCE :—The starches and celluloses constitute the polyoses ; they occur widely distributed in nature—in animals and in plants. They serve as reserve food, and as structural material. Glycogen, inuline and starch function as reserve carbohydrates, while cellulose constitutes the structural material for the cell walls in plants.

CLASSIFICATION :—The polyoses can be classifield according to the monosaccharose units produced by their hydrolysis : the ***hexosans*** ($C_6H_{10}O_5$) and the *pentosans* ($C_5H_8O_4$) ; the hexosans can be further subdivided into (i) glucosans which give glucose on hydrolysis *i e.* starch, glycogen, cellulose, etc., (ii) fructosans *e.g.* inulin, mannosans and (iv) galactosans. The most common pentosans which give pentoses on hydrolysis are araben and xylan.

GENERAL COMPOSITION AND BEHAVIOUR OF HEXOSANS :— Their chemical composition is expressed byt heformula $(C_6H_{10}O_5)n$, where the exact value of *n* is unknown. They are highly complex molecules with unknown and large molecular weights. They are amorphous and tasteless. A few of them like inulin, glycogen and starch are soluble in hot water ; cellulose on the other hand is quite

insoluble. The recent X-ray spectrographical evidence indicates definitely that the majority of them with the exception of glycogen are crystalline in strucrure. On hydrolysis by dilute acids or enzymes they yield monosaccharoses. Those from the animal source, give only glucose, while those derived from plants yield in addition to glucose, other monosaccharoses which may be either a different hexose molecule or a pentose. As hydroxylic (alcoholic) compounds, they form esters with organic and inorganic acids ; the well known esters are the acetates, nitrates, phosphates etc.

GENERAL METHODS OF INVESTIGATION OF CONSTITUTION :- These involve : (a) the determination of the basic unit or units present, (b) the mode linking of these units, and (c) the chain length of the molecules or the molecular weight.

(a) THE BASIC UNIT :—The fundamental procedure is to subject the complex poly-saccharose to a degradation process. This process is one of gradual depolymerisation of the initial molecule, $(C_6H_{10}O_5)n$ through various stages, in which *n* becomes smaller till the final product represents the C_6 unit i. e. a monosaccharose molecule. The degradation may be achieved by acid hydrolysis or by enzymes; in the latter case, the reversible action of the enzyme introduces a new complication; the products of such a degradation are not actually the direct fission products, but include the synthetic products formed by the combination of the simpler cleavege prducts. Number of typical bioses have been isolated as the products of such hydrolysis: starch and glycogen yield maltose, and cellulose gives cello-biose. Another biose encountered in some poly-saccharoses is gentiobiose.

(b) THE MODE OF LINKING —The methylation studies of the poly-saccharoses have given very important results regarding the mode of linking of the possible basic units, and the molecular structure of the basic hexose residue. Such studies, however, involve great difficulties and much labour. The alkylation of the complex polyoses proceeds extremely slowly, probably due to steric effects, and some of the hydroxyl groups present in the molecule escape methylation. The actual preseuce of hydroxyl groups in methylation. The actual presence of hydroxyl groups in methylated molecules can be established by reaction with acetic anhydride.

(*c*) THE MOLECULAR WEIGHT:—The determination of the molecular weights of macromolecules such as the starches, celluloses and the proteins, continue to tax the ingenuity of chemists. Several phyisical and chemical methods based on different principles, have been developed and perfected. Yet it must be admitted that the conclusions, reached by any one of these methods, are not decisive.

PHYSICAL METHODS:—The usual methods, depending on the measurment of the depression of the freezing-point or elevation of the boiling point, used for small molecules are not applicable to macromolecules like cellulose and starch. With the latter, the high molecular weight means that a high concentration must be used to have a measurable change in temperature. But the concentration becomes so high that van't Hoff's equation cannot be applied. There are three methods that are used now; they are based on (a) osmotic pressure, (b) viscosity and (c) sedimentation in an ultra centrifuge field.

The osmotic pressure method, developed by Meyer, is not easy; several measurements are necessary to extrapolate to infinite dilution; further, the method is limited, because of the lack of suitable solvents for solution of the macromolecules. Thus this method has been applied to the derivatives of cellulose and not to cellulose.

The viscosity method of Staudinger, is based on the observation that the viscosity of solutions of macromolecules is proportional to the molecular weight. The determinations of viscosities are easily made and hence this method is very frequently employed. However, it must be recognised that the values obtained represent only approximations.

The relation is expressed by the equation:

$$\frac{\mu_{sp.}}{C_{gm.}} = K_{m}.\ M.$$

$K_{m.}$ = a constant for each polymeric series.
$C_{gm.}$ = concentration of the solution in basic moles per litre.
$\mu_{sp.}$ = specific vyscosity.
= molecular weight of the compound.

The ultra centrifuge method due to Svedberg, has been used for cellulose and proteins; the solution of the macromolecule is rotated at a tremendous speed, so that it is subjected to a force of a million times that of gravity. Under this force, the particles tend to settle at

the bottom, at a rate which is proportional to their size. When equilibrium is established, the concentration of the solution, through the depth of the solution, is measured by determining the refractive index. Theoretically, the determinations made by this method appear to be the soundest but in practice, it is rather difficult to interpret the results.

It must be mentioned that the values obtained by these three methods are in very good agreement with those obtained by one another.

CHEMICAL METHODS :—These methods depend on the specific reaction of the 'end-groups' and hence are referred to as "End-group Assays."

The polyose molecule is built up of several glucose molecules linked together glycosidically and present as long chains. The extreme right end of the chain will carry a glucose residue which is unsubstituted on C_1. Such a residue will have a few specific reactions :

(i) It will reduce Fehling's solution. Bergmann developed a method in which the amount of reduction was estimated; the estimate would be a measure of the chain length. However the results obtained were always very low, probably owing to oxidation in other parts of the molecule.

(ii) It will give rise to one molecule of tetramethyl glucose, the other glucose residues present will yield trimethyl glucose molecules. Hence the chain length of the methylated molecule (cellulose) can be determined by calculyting the proportion of tetramethyl to trimethyl glucose. The method has some practical limitations; for it may not be possible to completely methylate the molecule, as in the case of cellulose, without causing some degradation.

(iii) It will react with C_2H_5SH in presence of HCl gas to from a mercaptal. In a method utilising this property, cellulose is added to HCl containing C_2H_5SH. With the progress of hydrolysis, more and more such glucose residues are produced and they react with the mercaptan to from the mercaptal. At specific intervals of time, samples are taken and analysed for sulphur content. In this

way, a fair measure of the end groups can be obtained. However, the results obtained by this method are usually low, probably owing to the rapidity of the initial reaction.

(iv) It will react with periodic acid to give formic acid; the latter can be measured by titration and hence the number of end-groups can be readily determined. A method based on such oxidations, was developed by Hirst and can be said to be the most reliable of all the chemical methods.

Lastly, the X-ray spectrographic diagrams have been used to corroborate the chemical evidence regarding the skeletal structures of the poly-saccharoses.

STARCH

Starch occurs chiefly in seeds and tubers of plants and to a small extent in leaves and fruits. It is an amorphous white powder insoluble in cold water; with iodine it gives a blue colouration.

CONSTITUTION OF STARCH :—Starch consists of two similar polysaccharoses : amylose contained in the starch cells and the amylopectin contained in the walls. Amylose dissolves in water without the formation of a paste and gives a blue colouration with iodine. It is hydrolysed by amylase quantitatively into maltose. The formation of paste – gelatinisation, is associated with amylo-pectin. It gives a violet colour with iodine and on hydrolysis with amylase, it forms a mixture of maltose and a tri-saccharose $C_{18}H_{32}O_{16}$ (Pringsheim). There is evidence to show that amylo-pectin, in addition, contains a small quantity of combined phosphoric acid.

SEPARATION OF THE TWO FRACTIONS :—The hot dilute solution of starch is treated with butyl alcohol, and allowed to cool; the amylose crystallises out as a complex with butyl alcohol, and amylopectin remains in the mother liquor and is precipitated out by the addition of alcohol.

AMYLOSE :—The soluble component (10-20%), on hydrolysis with dilute acids, yield, glucose only; while with the enzyme amylase it is partially hydrolysed to maltose. The results of methylation studies, also reveal the presence of a maltose unit. The molecular weight of amylose as determined by the osmotic pressure method ranges from 10,000–50,000.

Thus amylose is composed of unbranched chains of 1–4 linked glucopyranose residues with an α-glycosidic link. The length of the chain, as determined by the end group methods and by the osmotic pressure method varies from 100–500 glucose units, depending on the variety of starch. There is only one end group per molecule, which gives tetramethyl glucose. Amylose therefore is an unbranched polymer of glucose. This is further confirmed by the fact that amylose acetate, like cellulose acetate can be made into strong films and threads—a characteristic of linear polymers. X-ray studies indicate that amylose molecules are wound in spiral--an arrangement favoured by α glucoside linkages.

It has been recently reported that pure β amylase can effect only '70% fission of natural amylose into maltose. It is the mixture of β amylase and Z enzyme that can bring about 100% hydrolysis of amylose into maltose. Z enzyme specifically hydrolysis 1, 3′ glucosidic linkages. Therefore, it is now suggested that : amylose contains some 1.3′ linkages in addition to the main 1, 4' type of linkages.

AMYLOPECTIN :—This is the major component (80-90%) of all starches. In the waxy varieties of starch, the amylose content is less than 1%. On acid hydrolysis, amylopectin yields glucose only ; while the enzyme, amylase hydrolyses it to the extent of 60% only. The molecular weight as determined by osmotic pressure method ranges from 500,000–1000,000. The molecule of amylopectin is built up of several thousand α-glucose units. As in amylose, they are 1·4 linked, but the molecule is highly branched. This is based on the following analytical evidence :

(*a*) The end group assay shows that one end group for each 24-30 glucose units is present :

(*b*) Methylated amylopectin, on hydrolysis, gives (i) 2, 3, 6 trimethyl glucose, as the mian product, (ii) small amounts of 2, 3, 4, 6 tetra-methyl glucose, which corresponds to the end groups, and (iii) 2, 3 dimethyl glucose. The isolation of the last compound indicates that the chain is branched and that the branching occurs at the 6 position ; positions 1 and 4 are involved in the formation of the straight chain. Thus the amylopectin molecule contains a long main chain (1 – 4′ linkages) with branches at regular intervals joined by α 1 – 6′ linkages.

Thus the molecular structure is made up of a large number of short units which are constituted as amylose, but contain only 20 glucose residues. The short chains are joined to one another by a glycosidic linkage between the reducing end group of one unit and C_6 of one of the central glucose residues in another.

```
 C                  F
 G  ,  G......G     G  ,  G......G
 1     41     4     1     41     4
              |                  |
              |                  |
              4                  4
 G......G......G ,  G......G  ,  G  ,  G
 14     14     16   14     14    16    14
 A             B    D            E
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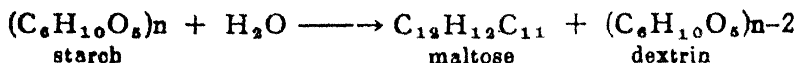
ABC, DEF are the chains containing 20, 1–4 linked glucose residues. They are joined together at B and E by 6–1 links. The non-reducing terminal glucose residues are present at C and F.

Thus amylopectin is represented as a long chain molecule, possessing numerous, short side chains. The highly branched structure explains readily, why amylopectin acetate, though of high molecular weight does not form threads or films. It also accounts for the tendency of the amylopectin molecules, not to aggregate or crystallise as amylose ones do. Hence also there is no retrogradation as in the case of amylose.

SYNTHETIC STARCH :—Hanes has reported the conversion in good yields of glucose–1–phosphate into a starch-like product by an enzyme preparation from potato juice. This synthetic product is similar to amylose; it gives blue colour with iodine, and is converted by amylase into maltose. Peat, on the other hand, has obtained a synthetic product similar to amylopectin, from glucose–1 phosphate and another enzyme prepared from potato juice.

DEXTRIN :—It is product of partial hydrolysis of starch by the action of *diastase*; it is a white powder which dissolves in water to form a gummy solution; it is dextro-rotatory hence the name; it possesses slight reducing properties. With dilute I_2 solution, it gives a reddish brown colouration. It can be completely hydrolysed by boiling with dilute acids into glucose.

COMPOSITION AND STRUCTURE :—The partial hydrolysis of starch to give dextrin is accompanied by the formation of a molecule of maltose.



$$\underset{\text{starch}}{(C_6H_{10}O_5)n} + H_2O \longrightarrow \underset{\text{maltose}}{C_{12}H_{12}C_{11}} + \underset{\text{dextrin}}{(C_6H_{10}O_5)n\text{-}2}$$

Hence it follows that dextrin molecule contains two glucose units *less* than the starch molecule. The exact manner in which the two glucose units are removed is not yet known. Further the structural formula for dextrin must be capable of accounting for the observed reducing properties. Starch does not possess any reducing property.

CELLULOSE

Cellulose is the most plentiful of all organic compounds occurring in nature. It constitutes the skeletal material of plants. It is a highly complex compound of unknown molecular weight. It is represented by the formula $(C_6H_{10}O_5)x$. It is insoluble in most solvents, but dissolves in cuprammonium hydroxide and can be reprecipitated by acids. It dissolves in a solution of $ZnCl_2$ in HCl.

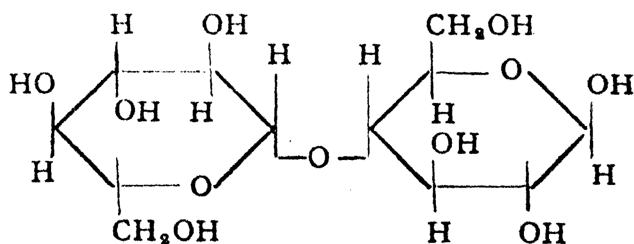
Cotton is the purest form of cellulose. Plant celluloses are not usuall homogeneous and can be purified by treatment with NaOH, which dissolves the impurities present. The celluloses have been classified as : α, β, or γ celluloses on the basis of relative solubility of the cellulose in varying concentration of NaOH. (17–18%)..

CONSTITUTION :—Many attempts have been made to unravel the chemical structure of the complex molecule. But so far, it has not been possible to arrive at a complete understanding of the chemical nature of the cellulose molecule. A large amount of research based on new principles and technique has been carried out to discover the structural unit lying at the basis of this complex poly saccharose. As a result, it is now known that cellulose is largly built up of glucose units. However, the exact number of such units and their mode of linking to build up the entire poly-saccharose pattern are still undetermined. A brief summary of pioneer researches of the Birmingham School led by Haworth in England, and of Staudinger, Freudenberg and Karrer in Germany will be given below.

For a long time, the following four facts, very significant from the stand-point of the structural chemistry of cellulose were known :

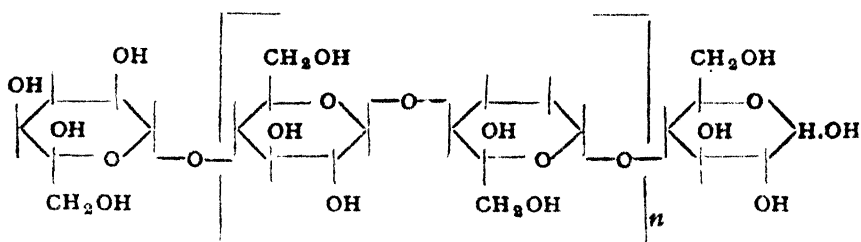
—(i) Cellulose contains no free aldehydic group. (ii) The product of acid hydrolysis of cellulose is *D*-glucose. (ii) Acetolysis (action of concentrated sulphuric acid and acetic anhydride) of cellulose gives an acetate of a biose, cello-biose. (iv) There are three free hydroxyl groups only, which can be esterified or methylated. These facts definitely indicate that cellulose is built up entirely of glucose units, but the more difficult problem is how these glucose units are linked together and whether the same mode of linking persists throughout the entire chain of molecule.

THE BASIC UNIT OF THE CELLULSE MOLECULE :—The mode of attack was to break down the complex poly–saccharose into simpler oligo saccharoses. Cello-biose was isolated as the product of acetolysis of cellulose and a structure in which this biose is the repeating unit, was proposed for cellulose. A doubt was raised that, the biose is not present as such in the cellulose molecule, but is a reversion product, as two molecules of glucose formed by the hydrolysis of the cellulose may unite to give the biose under the influence of an enzyme. To settle these points, : methylated cellulose has been degraded under conditions and by the use of reagents which are known to have no synthetic action on glucose. Thus, methylated cellulose was treated with acetyl bromide in chloroform at 16°. A partly methylated cellobiose was formed. Oxidation, methylalation and subsequent hydrolysis of the ester gave *n*-tetra-methyl glucose and 2-3-5-6-tetra-methyl gluconic acid. These results showed that the position 4 of gluconic acid was linked with the position 1 of glucose residue in cello-bisoe. It was, thus, established that cello-biose is present in cellulose molecule. In 1926, Haworth and his collaborators advanced a complete proof of the structure of cell-biose by methylation studies. At the same time, Zamplen achieved a synthesis of cello-biose by way of the cyanohydrin reaction, which supported Haworth's structure.



Cellobiose

The isolation of 2, 3, 4, 6-tetra-methyl glucose as one of the products of hydrolysis of tri-methyl cellulose, indicated an oper chain structure for the cellulose molecue in which the cello-biosa units are repeated:—



THE LENGTH OF THE CHAIN :—In such a formula the length of the chain is roughly indicated by the proportion of tetramethyl glucose. On this basis, Haworth and Machemer have shown that the chain consists of not more than 200 and not less than 100 glucose units. However, this method of determining the length of the chain rests on the assumption that the amount of hydrolysis and the isolation of tetra-methyl glucose are approximately quantitative.

The molecular weight of cellulose has been estimated by the following method : (1) The end group assay method depending on the cleavage (oxidation) by periodic acid ; (2) The viscosity method, (3) The osmotic pressure method. The results of all these methods indicate values which range from 300,000–500,000.

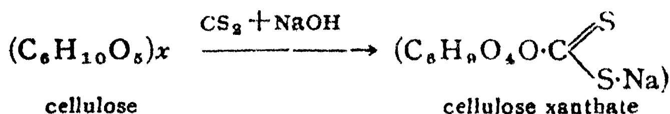
CONTINUITY OF THE LINKAGE :—In the foregoing, it has been assumed that the cello-biose link persists throughout the cellulose chain. Haworth and his collaborators have adduced conclusive evidence in support of the assumption. For this purpose, cellodextrins, containing four or more glucose residues have been investigated, Willstatter, Zechmeister, Irvincost and others were able to isolate in addition to cello-biose, other oligo-saccharoses, *e. g.*, cello-triose and cello-tetrose. These were methylated and degraded by acetyl bromide in chloroform at 16°. Cello-tetrose under these conditions gave *n*-tetra-methyl glucose and a completely methylated cello-triose which was crystalline. The methyl cello-triose was in turn degraded to octa-methyl cello-biose and *n*-tetra-methyl glucose. These results clearly reveal that four continuous units of the cellulose chains are united in the same manner as cello-

biose. That the linkages between the individual glucose units are the same, has been proved in the following way.

Derivaties of cello-biose and cello-triose were synthetically obtained by allowing 2-3-6-tri-methyl β-methyl glucoside to react on the chlorohydrins of premethylated glucose and cello-biose. These syntheses established the nature of the linkages in the oligo-saccharoses; and by a determination of the values of optical rotation and evaluation of the optical superposition. Freudenberg proved that all the glucosidic linkages in the different oligo-saccharoses, cello-triose and cello-tetrose were the same, and β glucosidic in nature. Freudenberg and Kuhn by the kinetic experiments of the hydrolysis and acetolysis of cellulose have provided further evidenoe in support of the fact that there is only one type of linkage between the individual glucose units of the cellulose molecule. X-ray evidence also gives confirmation of the above formulation. This evidence was first brought forward by Sponsle and later on by Meyer and Mark. The length of the unit cell along the chain axis, which is called the frequency period, is 10·3A°; the value for cello-biose unit is 10·25A°. This shows that the chains are straight with respect to the fibre axis. The X-ray examination of the cellulose fibre, further shows crystalline regions. They are accounted for by the micellar theory, which postulates that the crystalline supermolecular unit is made up of micelles *i. e.* bundles of parallaled orientated chains. The width of a micellar unit is 60°A, which corresponds to 10–20 cellulose chains; the length of the unit is 600°A which corresponds to chain length of 200 glucose units.

SYTHETIC CELLULOSE :—Hibbert has achieved a synthesis of cellulose by the action of Acetobacter xylinium on glucose.

REGENERATED CELLULOSE AND CELLULOSE DERIVATIES :—Cellulose is a natural macromolecule, with specific physical properties that make it valuable as fibre. However, some of the wood celluloses have fibres, which are too short for direct spinning and hence have to be regenerated. There are two methods of regeneration: in one method, the wood cellulose is dissolved in cuprammonium hydroxide and is reprecipitated by acids. In the other, cellulose is made to dissolve in carbon disulphide in presence of alkali; probably, a salt of the xanthic acid is formed. Probably, the CH_2OH group is xanthogenated.



$$(C_6H_{10}O_5)x \xrightarrow{CS_2 + NaOH} (C_6H_9O_4O{\cdot}C{<}^{S}_{S{\cdot}Na})$$

cellulose — cellulose xanthate

On standing, the solution of cellulose xanthate ages and its viscosity goes on increasing. On account of its high viscosity, it is called *viscose*, and under that name it is used in the manufacture of *viscose rayon*, a kind of artificial silk.

Lastly we have the mercerised cellulose. With concentrated alkali, cellulose suffers a change such that it wrinkles up, but shows a peculiar lustre and a great tendency to absorb dyes. The process was developed by Mercer and is known as *mercerisation*. It is of great practical importance in the textile industry.

We have seen that cellulose is a natural macromolecule, built up of a large number of glucose units. It is colloidal in nature and exhibits general insolubility. Much effort has now been expended to develop synthetic derivatives, of cellulose, which do not possess these undesirable and inconvenient properties. Cellulose is a hydroxylic compound and hence the main derivatives prepared are (i) the esters and (ii) ether. The cellulose nitrate and cellulose acetate are the two esters, manufactured on a large-scale and used as explosives, plastics and textiles. Other esters like propionates, butyrates, strearates etc. are being prepared and investigated for use as potential fibres and plastics. Methyl and ethyl celluloses are the two ethers which are also attrating some attention as synthetics. Oxidation of cellulose with nitric acid gives oxalic acid.

GLYCOGEN :—It is the reserve material of animals. Ii is a white powder; it forms an opalescent solution with water and gives with iodine, a reddish-brown colour. On hydrolysis with acids, it is converted into glucose. Hydrolysis of the merhylated product gives 2, 3, 6, trimethyl glucose as the chief product, along with equal amounts of 2, 3 dimethyl glucose, and 2, 3, 4, 6-tetramethyl glucose. These results indicate that glycogen is similar to amylopectin; but probably the branches are shorter.

INULIN :—It occurs in dahlia and jerusalem artichoke tubers. On scid hydrolysis, it gives *D*-fructose only. The results of methylation studies indicate that inulin molecule is built up of unbranched *D*-fructo-furanoside units linked from C_1 to C_2. The configuration of the glycosidic link is not known.

HEMI-CELLULOSES :—They are the pentosans, xylan and araban; on hydrolysis, they give pentoses. They may have a few hexose units condensed with the pentoses. They are thus classified as hetero-polymers. They are closely associated with cellulose, in nature. They are differentiated from cellulose by being more readily hydrolysed by acids; they also more readily dissolve in alkalies; xylose, in xylan is present in the pyranose form. The molecular weight as determined by the viscosity method corresponds to about 100 xylose units in the molecule.

POLYURONIDES :—They are the polymers built up of several uronic acid molecules. Alginic acid, from the seaweeds is an important member of this group. It is usually isolated as its Na-salt. On acid hydrolysis, alginic acid gives *D*-mannuronic acid as the sole product. Methylation is difficult; but the relatively great stability towards acids indicates a pyranoside formulation. It readily forms threads and hence, it must be a linear polymer. Thus alginic acid is built up of *D*-mannuronic acid units joined together from C_1 to C_4; the glycosidic combination is β; the molecular weight is of the same order as that of cellulose.

Na-alginate is rapidly becoming an article of commerce. It finds use as a thickening agent, in the preparation of custard. An important use is in the manufacture of textiles. Other uses include the making of high grade adhesives, photographic films and shatter-proof glass.

Pectin is another polyuronide; it gives on acid hydrolysis, *D*-galacturonic acid and CH_3OH in amounts which indicate that the repeating unit is D-galacturonic acid; and that some of these units are present as methyl esters. It is stable to acid; hence the hexuronic acid units must be pyranose. The glycosidic linking is from C_1 to C_4 and has probably the α configuration. The setting of jams and jellies is caused by pectin. Fruits like lemons, applies, grape fruit with a high pectin content, make preserves which set readily.

Lastly the gums and mucilages which are widely distributed in the plants are highly complex compounds, related to polyuronides, because on hydrolysis, they give uronic acids and sugars. They are thus hetero polymers, built up of heterogeneous units like hexoses and hexuronic residues.

CHAPTER II

TANNINS AND DEPSIDES

INTRODUCTION :—Tannins are a group of complex, mostly amorphous organic compounds of vegetable orign. They occur widely distributed in the vegetable kingdom. They are present in large amounts in gall-nuts, and in the barks of many trees *e. g.* Oak. Wattle, Hemlock, Horse-chestnut ; Sumach, tea myrabolan nuts, the wood of Acacia catechu and the bark of twigs of Cassia auriculata (south India) contain some of the technically important tannins.

GENERAL COMPOSITION AND PROPERTIES :—The tannins contain carbon, hydrogen and oxygen and structurally belong to different types. The most common of them are the esters. They are classified as glycosides ; on hydrolysis they yield glucose and tannic acids. The typical tannic acids are; protocatechuic acid (3, 4-dihydroxy benzoic acid), gallic acid, and m-digallic acid: they are all hydroxy-benzoic acids.

The tannins as a class are characterised by the following properties ; (i) They are astringent and they act as negatively charged colloids. (ii) They combine with the protein of the animal hide or with gelatin to render it pliant and non-putrescible ; they convert raw hides into leather. This is the basis of the commercial process of tanning the hides (iii) They give with ferric salts a blue-black or green colouration of precipitate. This property is utilised in the manufacture of the common inks.

CLASSIFICATION —Our knowledge of the chemical constitution of tannins is still incomplete and hence a rational, chemical classification has not been so far possible. However, one may divide them into three classes, based on the fundamental phenolic unit present in their molecules. Thus, we have :

(*a*) THE PYROGALLOL TANNINS :—They include the gall chestnut and oak wood tannins. They contain the structural unit, pyrogallol. These tannins possess the following characteristics : (i) they give a dark-blue colouration with ferric salts, (ii) they give no precipitate with bromine water and (iii) they produce on leather a 'bloom' consisting of ellagic acid. The latter is closely related to gallic acid and is obtained from it, by heating with arsenic acid.

(*b*) THE PYRO-CATECHOL TANNINS:—These include the tannins obtained from pine barks, mimosas, oak barks, mangrove barks and gambia . Their structural unit is the catechol unit. They are further characterised by (i) the formation of a green-black precipitate with ferric salts (iron alum); (ii) the formation of a yellow or brown precipitate with bromine water and (iii) the non-formation of a bloom on leather.

(*c*) THE PHLOROGLUCINOL TANNINS:—These tannins result from the hydrolysis of the *catechins*. They are amorphous and colloidal. They are found in catechu, gambier catechu, and many other commercial catechus. They contain the phloroglucinol unit. When an aqueous solution of a catechin is heated, a colloidal tannin is formed. Hot mineral acids, on the other hand, give an amorphous, insoluble precipitate which is called tannin red. Genetically and structurally, the catechins are closely related to flavonols. The tannin reds are phlobaphene; the tannins of this class are therefore called *phloba-tannins*.

Recently, a more comprehensive classification has been suggested. According to this classification, we have :

(*a*) DEPSIDE TANNINS :—They comprise the gall tannins which are structurally esters and on hydrolysis give glucose and gallic acid. They are further subdivided into (i) pyragallol and (ii) catechol tannins.

(*b*) ELLAGIC TANNINS :—They give on hydrolysis with dilute acids glucose and ellagic acid. Such tannins occur in certain nuts and pods.

(*c*) PHLOBA TANNINS :—They occur in the wood, bark, leaves and roots of plants ; they include the most important tanning materials. On hydrolysis, they yield phloroglucinol and gallic acid. They are related thus structurally to benzopyran—flavonol unit.

ISOLATIDN OF THE TANNINS :—There are two principal methods depending on two different principles :

(*a*) THE LEAD ACETATE METHOD :—In this method the tannin is precipitated out. The raw material is digested with hot water in which the tannins are soluble. Lead acetate is then added when the tannins are completely precipitated out. The precipitate is

then decomposed by H_2S to remove lead as PbS, and the tannin solution is concentrated in vacuo.

(*b*) THE EXTRACTION METHOD:—This method involves the use of specific organic solvents. In this method, organic solvents are employed for the extraction of the tannins. Various mixtures of alcohol, water and ether are used; but acetone appears to be the best solvent so far, Ethyl acetate is also finding an extensive application. In all cases, the extraction of the tannin is carried out from an alkaline medium (*cf.* Fischer's isolation of chinese tannin). The preparation of the tanning material from the natural sources is as follows: the aqueous extract of the bark etc. is evaporated in multiple-effect film evaporators, under reduced pressure; the solid extract containing 50-60% of tannins and very little insoluble matter is put in the market.

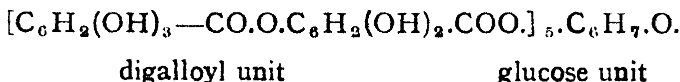
CHINESE TANNIN

The most typical and important tannin is the *tannic acid* of commerce. It is obtained from the chinese gall-nuts and hence, known as chinese tannin or gallo-tannin. The powdered gall-nut is dissolved in Na_2CO_3 excess and solution extracted with ethyl acetate. It is a colourless amorphous compound soluble in water, but sparingly soluble in alcohol or ether. Its aqueous solution is bitter and astringent and with ferric salts gives a dark-blue colouration. An animal hide is tanned and converted into leather by an aqueous solution of tannin. The use of tannic acid solution (1%) in the treatment of burns, is also based on its property of reacting with proteins.

The present constitution of this natural product is based on the extensive researches of Fischer, Freudenberg and collaborators. As early as 1852, Strecker isolated the tannin from the gall-nuts and represented it by the molecular formula $C_{27}H_{22}O_{17}$. He further considered it to be built up of one molecule of glucose and *three* molecules of a hydroxy acid, gallic acid. However, these conclusions lacked sound experimental basis and Fischer reopened the whole question of the constitution and started afresh to attack it in his usual masterly way.

Fischer and Freudenberg prepared a sample of gallotanin, by extraction from a weak alkaline solution with ethyl acetate. The

product is an amorphous powder and there is no conclusive evidence for its purity. However, the same sample was obtained from diffe rent sources. On hydrolysis of the product, with 5 per cent sulphuric acid at 100°C, the following results were obtained: (*a*) glucose, 7-8 per cent, and (*b*) gallic acid, 93–92 per cent. No other hydroxy acid was detected among the products of hydrolysis. Fischer concluded that the tannin molecule contained one molecule of glucose in combination with *ten* molecules of gallic acid. But glucose contains only five hydroxyl groups, which could unite with five of the ten acyl radicals of the ten gallic acid molecules. The ten gallic acid units must therefore be so present as to offer only *five* acyl groups. The simplest and most probable mode of combination would be the formation of five digallic units. The other possibilities viz. the presence of trigallic or tetra gallic acid units, were not taken into consideration at all. Tannin was therefore represented as penta-digalloyl-glucose :—



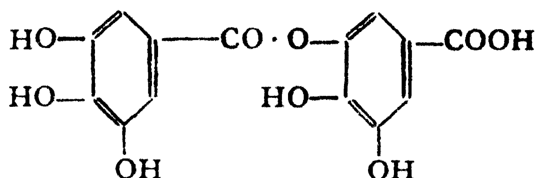
$$[C_6H_2(OH)_3\text{—}CO.O.C_6H_2(OH)_2.COO.]_5.C_6H_7.O.$$

digalloyl unit glucose unit

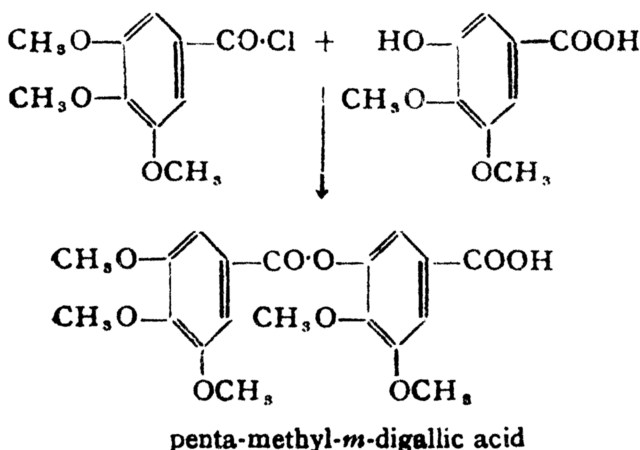
Thus, the unit linked with glucose in the tannin formation is the digalloyl unit obtained by the elimination of one molecule of water from two molecules of gallic acid by way of *ester* formation. Theoretically, two digalloyl units (meta or para) are possible. Fischer made several attempts to isolate the digalloyl unit present, but met with failure. All the usual methods of hydrolysis would break both the glucosidic combination and the ester linking between the two gallic acid units, and effect a total cleavage of the complex molecule into its simpler constituents.

Fischer, with great foresight then turned his attention to the synthetic method of approach. Herzig and his collaborators had reported the preparation of a methyl-tannin by the action of diazo methane on the natural gallo-tannin. On hydrolysis, it gave tri-methyl gallic acid, *m*-*p*-dimethyl gallic acid and glucose. The formation of the unsymmetrical *m*-*p*-dimethyl gallic acid, indicates that one of the three *OH* groups of one of the gallic acid molecules must have been involved in the ester formation, as it has escaped methylation. Further, it is one of the two *meta* hydroxyl groups. Therefore, the

digallic acid unit present in the tannin molecule must be the *m*-digallic acid unit :



SYNTHESIS OF METHYL TANNIN :—Fischer's next step was to obtain such a unit and then synthesise the tannin that can be compared with the natural product. He first synthesised the methyl tannin in the following way. The penta-methyl-*m*-digallic acid was first obtained by the condensation of trimethyl-galloyl chloride with *m*-*p*-dimethyl-gallic acid in the presence of *NaOH* :



penta-methyl-*m*-digallic acid

The chloride of this acid was then condensed with the two forms-α and β-of glucose. The corresponding α and β-(penta-methyl *m*-digalloyl) glucoses were obtained. These synthetic products showed very close resemblance to the product obtained by the methylation of the natural tannin *i. e.* Herzig's *methyl-tannin.*

THE SYNTHESIS OF THE NATURAL TANNIN :—The analytical evidence clearly indicated that the natural tannin was probably the penta-*m*-digalloyl glucose. The synthesis of this susbtance was delayed for want of a method of preparing partially protected gallic acid molecules, required for the synthesis of *m*-digallic acid. The

factors that influence the choice of a particular protecting group are :—

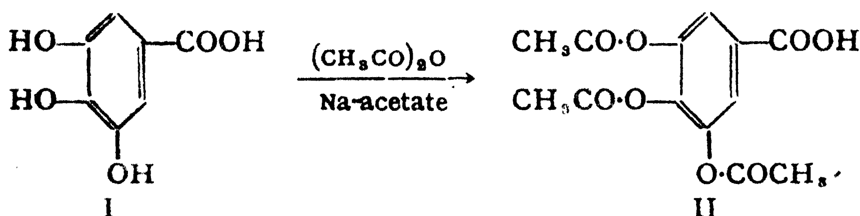
(*a*) The group must be readily introduced.

(*b*) It must be capable of ready elimination.

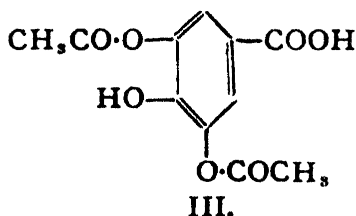
(*c*) It must improve the crystallisability of the compound.

These considerations limit the choice to (i) acetyl, (ii) benzoyl and (iii) $COOCH_3$ (carbo-methoxy) and $COOC_2H_5$ (carbo-ethoxy) groups. Of these, only the acetylation method was fully developed by Fischer after a long period of systematic research; and he was finally able to synthesise the natural tannin. The various steps in the process are :—

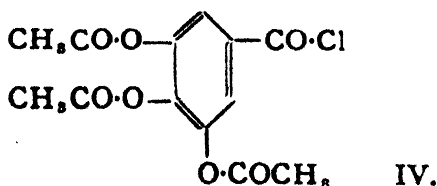
SYNTHESIS OF *m*-DIGALLIC ACID :—Gallic acid was first fully acetylated with acetic anhydride to give the tri-acetyl gallic acid.



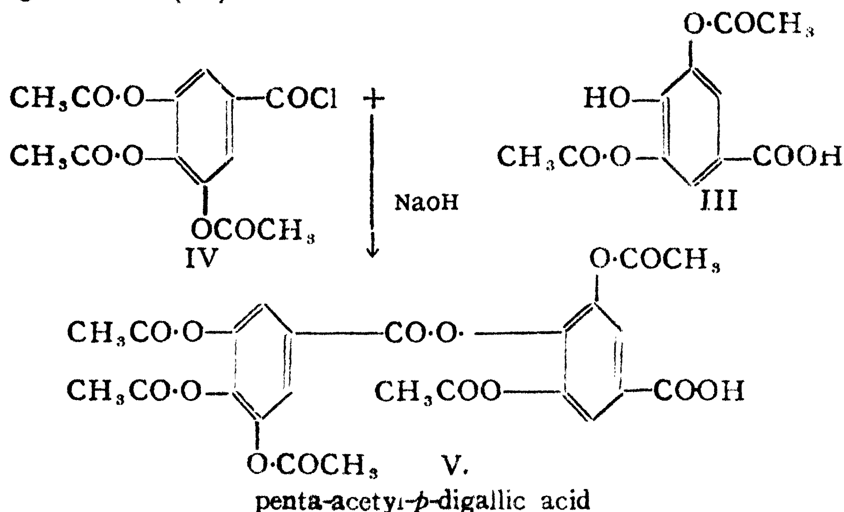
By partial hydrolysis, (II) was converted into *m*-*m*-diacetyl gallic acid (III)



Another molecule of triacetyl gallic acid (II) was changed into its chloride (IV), by the action of PCl_5.



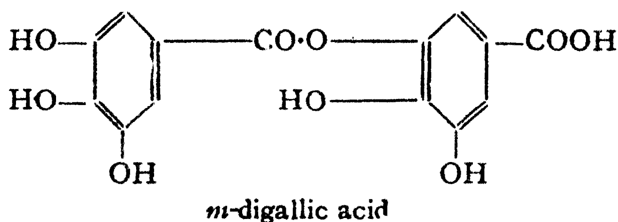
The triacetyl-gallic chloride (IV) was then condensed with the diacetyl acid (III), in presence of NaOH to give the penta-acetyl-digallic acid (V).



penta-acetyl-*p*-digallic acid

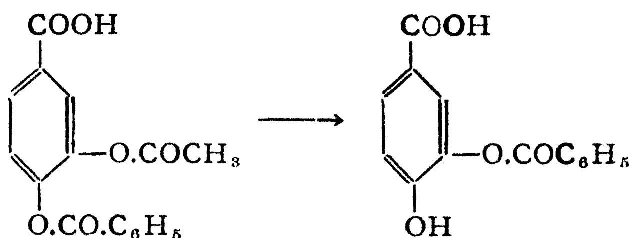
The penta-acetyl-*p*-digallic acid was converted into the *m*-digallic acid by hydrolysis, which involves a rearrangement reaction.

m-Digallic acid is a crystalline compound melting at 285°C. It has a bitter taste which afterwards becomes sweet. It has the following structure :—

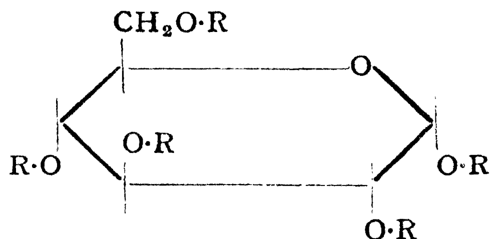


m-digallic acid

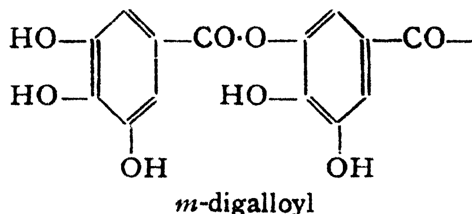
The theoretically obvious *para*-digallic acid is not formed at all. Fischer has shown that this is due to a wandering of the galloyl radical from the *para* to the *meta* position during the hydrolysis of the acetyl groups. This migration is however not limited to the galloyl radical; a benzoyl radical has also been shown to wander in exactly the same way. When *p*-benzoyl-*m*-acetyl proto-catechuic acid is hydrolysed, the elimination of the acetyl radical is accompanied by a subsequent migration of the benzoyl radical from the *para* position to the *meta* position.



SYNTHESIS OF THE TANNIN :—The *m*-digallic acid was acetylated and then converted into the acid chloride by the action of PCl_5 on the acetylated *m*-digallic acid, in chloroform solution. The acid chloride was subsequently condensed with α and β glucose in presence of quinoline. The acetyl groups were finally removed by mild hydrolysis with alkali in the cold. After the completion of the hydrolysis, H_2SO_4 was added and the penta-*m*-digalloyl-glucose was shaken up with ethyl acetate. The potassium salt was then precipitated by the addition of *K*-acetate in absolute alcohol. The free penta-*m*-digalloyl glucose was liberated from its salt by the action of H_2SO_4 and finally extracted with ethyl acetate. Thus, it has the formula :—

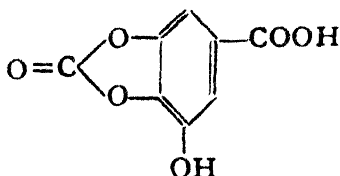


where R =



m-digalloyl

Subsequently great improvement in the technique of the protection of the hydroxyl groups of the gallic acid has been made. Thus, protection has been more successfully achieved by means of phosgene ($COCl_2$). Gallic acid, on treatment with $COCl_2$ in presence gives the partially protected 3–4–carbonate derivative :—



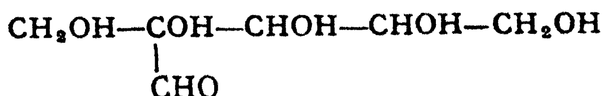
This is condensed with triacetyl-galloyl chloride (IV) (see p. 134) to give a compound, which on hydrolysis with NH_4OH at 0°C gives *m*-digallic acid. Lastly, the great technique of Bergmann, which employs ($C_6H_5CH_2$-*O-COCl*) as the protecting agent, promises to produce far-reaching results. This group can be readily removed by mild hydrogenation and thus the elimination can be achieved under condition, which hardly affect the *depside* linking (*CO.O.*) of these synthetic products.

Properties of penta-m-digalloyl-glucose (*α or β*) : It is a pale brown amorphous substance. It resembles very closely the natural product in amorphism, taste, solubility, acidity and colour reaction with $FeCl_3$. It also precipitates gelatin and alkaloids.

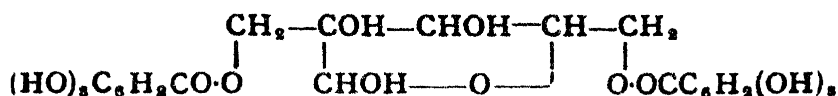
Recently it is suggested that the high molecular weight tannins contain an oligosaccharide *core*, which is esterified with galloyl and digalloyl groups. These suggestions are based on the enzymatic degradation of the tannins with esterases which remove the galloyl groups only, and leave behind the central carbohydrate core. However these suggestions have not been fully accepted by all workers in the field.

TURKISH TANNIN :—This is the tannin from the twig gall. It is closely related to chinese tannin and like the latter, is a galloylated glucose. On hydrolysis, it gives gallic acid and ellagic acid. The gallic acid content is smaller than in the case of chinese tannin. There are 5–6 molecules of gallic acid to one of glucose.

Another tannin of some importance has been isolated in crystalline form, from the bark of Hamamelis verginiana, by the use of enzyme tannase, by Freudenberg. It is a galloylated hexose. Freudenberg has shown that the sugar has the structure :—



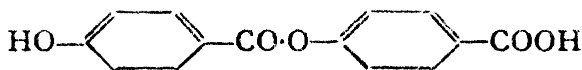
and the tannin is the digalloyl ester of this sugar :



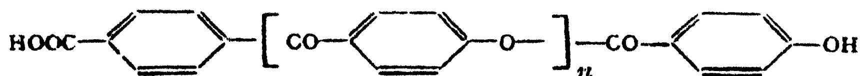
USES :—The tannins are technically very important compounds. They are used in large quantities in the manufacture of inks. In the textile industry, they find extensive application as mordants. Lastly, in the form of special preparations like tannabin, and tannoform, they are used in medicine.

SYNTHETIC SUBSTITUTES.

The investigations of the structure of the natural tannin had revealed that its molecule was built up of *m*-digallic acid units. The latter contained an ester group,—CO—O—and was formed by the esterification of the carboxyl group of a gallic acid molecule with the hydroxyl group of another gallic acid molecule. Earlier, Fischer had been investigating into the structure of proteins and the polypeptides and these studies, gave him the clue for which he had been looking for. He conceived the brilliant idea of synthesising a new series of chain compounds from hydroxy-benzoic acids. Two or more hydroxy acid molecules can be condensed together to form a depside. It will possess the structural unit :—



Such a structural unit bears great analogy to the *peptide* linking (*—CO—NH—*) present in the polypeptides. The latter compounds were also synthesized by Fischer in connection with his investigation on *proteins* and are built up by linking together in a chain, a series of molecules of α-amino-acids, each of which contains a *COOH* and an NH_2 group. This was the birth of a new class of compounds—the depsides—the synthetic substitutes of the natural product. These are polyesters and are chain compounds built up of hydroxy acid molecules. They possess the general formula :



But these could not replace the natural materials in the tanning processes. Hence attempts have been made to prepare synthetic

materials that could be used for tanning purposes; as the natural tannins are phenolic in nature, it is obvious that phenolic compounds should form the starting materials for such synthesis. This work has finally led to the synthesis of the *Syntans.* Thus we have two types of synthetic substitutes for tannins :—(a) the depsides and (b) the syntans.

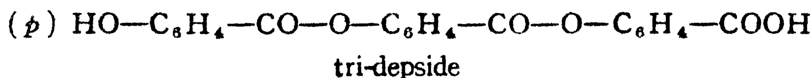
DEPSIDES

The depsides, thus originally represented a whole group of synthetic substances produced by Fischer and others in their laboratories. Like the natural tannins, they precipitated gelatin, gave a blue colouration with ferric salts, and thus showed great resemblance to them: hence Fischer coined for them, the class name depside (depside means to tan). The word also suggested a likeness to "the peptides" in the similarity of the presence of chains, in the molecules of the two types of compounds. The "lichen products" or "moss acid acids" are now known to contain a number of depsides derived from poly-hydroxy aromatic acids. The most important and typical ones that have been isolated are lecanoric acid and evernic acid.

NOMENCLATURE—The depsides are termed di-, tri-, tetra and so on, depending on the number of hydroxy acids involved in the condensation to give the depside. Thus we have :—



(*p*) $HO—C_6H_4—CO—O—C_6H_4—COOH$ di-depside,

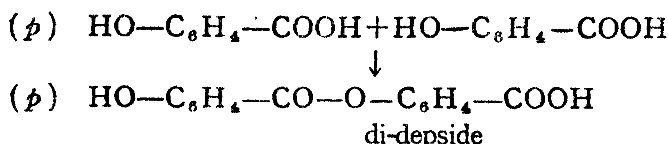


(*p*) $HO—C_6H_4—CO—O—C_6H_4—CO—O—C_6H_4—COOH$ tri-depside

GENERAL SYNTHETIC METHODS :—The problem of the synthesis of the depsides presents special difficulties. They are esters formed by the interaction of the acidic carboxyl group and the semi-acidic phenolic *OH* group. The operation is not simple and special methods have to be developed to effect such a linking and to obtain a suitable yield. Further, the ease of a depside synthesis is conditioned by the nature of the hydroxy-benzoic acids involved. Of the three mono-hydroxy benzoic acids, depside formation proceeds with great rapidity in the case of the *para* isomer only; the ortho compound

gives a depside with great difficulty. With poly-hydroxy benzoic acids, for example gallic acid, the depside formation may involve either the para-hydroxyl or one of the meta-hydroxyl groups and lead to a mixture of two depsides which is very difficult to separate. This necessitates the protection of some of the hydroxyl groups, leaving free only one hydroxyl group in a known position, thus giving a depside of known structure. To all these difficulties must be added the complications introduced by possible rearrangement reactions.

A simple di-depside can be formed from two molecules of *p*-hydroxy-benzoic acid and will have the formula :—



$$(p)\ HO{-}C_6H_4{-}COOH + HO{-}C_6H_4{-}COOH$$
$$\downarrow$$
$$(p)\ HO{-}C_6H_4{-}CO{-}O{-}C_6H_4{-}COOH$$

di-depside

The di-depside can be further condensed with another molecule of the same acid, to give the tri-depside :—



$$(p)\ HO{-}C_6H_4{-}CO{-}O{-}C_6H_4{-}CO{-}O{-}C_6H_4{-}COOH$$

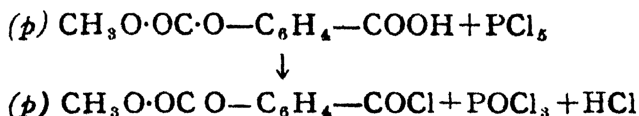
In order to obtain good yields in the preparation of the depside, the following general procedure is adopted :—

(i) One of the *OH* groups of the condensing molecules is put out of action or protected. Fischer first employed methyl chloroformic ester, $ClCOOCH_3$, in alkaline solution in the cold to obtain the *carbo-methoxy* derivatives. This radical can be readily introduced and equally readily eliminated by hydrolysis, under conditions which do not attack the depside linking—*CO—O—*.



$$HOOC{-}C_6H_4{-}OH\ (p) + Cl\,CO{\cdot}OCH_3 \rightarrow HOOC{-}C_6H_4{-}O{\cdot}CO{\cdot}OCH_3\ (p)$$

(ii) The methyl carbonate-(carbo methoxy) derivative is converted into the acid chloride by the action of PCl_5 in chloroform solution. The chloride is found to be a crystalline compound.



$$(p)\ CH_3O{\cdot}OC{\cdot}O{-}C_6H_4{-}COOH + PCl_5$$
$$\downarrow$$
$$(p)\ CH_3O{\cdot}OC\ O{-}C_6H_4{-}COCl + POCl_3 + HCl$$

(The preparation of the acid-chloride also necessitates the protection of the hydroxyl group).

(iii) The acid chloride in acetone solution, is then condensed with phenolic acid in the presence of *NaOH* in the cold, dimethylamine, or pyridine. The depside is then precipitated by the addition of a dilute mineral acid.



$$CH_3O{\cdot}OC{\cdot}O{-}C_6H_4{-}COCl + HO{-}C_6H_4{-}COONa$$



$$\downarrow$$



$$CH_3O{\cdot}OC{\cdot}O{-}C_6H_4{-}CO{-}O{-}C_6H_4COONa$$



$$\downarrow HCl$$



$$CH_3O{\cdot}OC{\cdot}O{\cdot}C_6H_4{-}CO{\cdot}O{\cdot}C_6H_4{\cdot}COOH$$

The protecting group is then removed by the action of dilute alkali like N·NaOH or Na_2CO_3 in the cold or by the action of ammonia in the presence of pyridine to give the depside $HO{\cdot}C_6H_4{-}CO{\cdot}O{\cdot}C_6H_4{\cdot}COOH$. These processes may be repeated to build up systematically the higher depsides. In later years, Fischer emgloyed the acetylation method of protecting the hydroxyl groups. The acetyl derivatives are easily prepared by shaking the phenolic acid with acetic anhydride in presence of $ZnCl_2$, dimethylaniline or pyridine. The acetyl-derivatives crystallise well and may be converted into their chlorides without difficulty. After condensation, the acetyl groups are removed by alkali *e. g.* K_2CO_3 solution at O°C or by NH_3 at the ordinary temperature. Na-acetate, can be used at a little high temperature to de-acetylate the compounds.

Depsides have also been obtained from di-and tri-hydroxy aromatic acids. Thus, the depsides of the following acids have been synthesised :—(*a*) proto-catechuic acid, (*b*) gallic acid, (*c*) β-resorcylic acid. The synthesis of depsides in these cases, involves the following operations :—(*a*) Preparation of partially protected hydroxy acids : There are *two* important methods of achieving this result.

First method :—The poly-hydroxy benzoic acid, *e.g.*, gallic acid is fully acetylated by shaking the acid with $(CH_3CO)_2O$ in the presence of pyridine. The fully acetylated product is then subject to controlled hydrolysis with sodium carbonate solution whereby one or

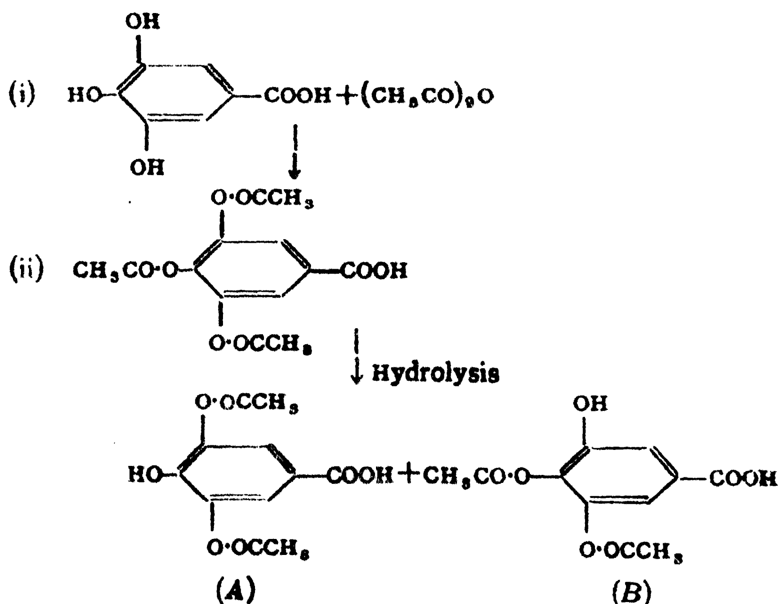
two of the acetyl groups are eliminated. The constitution of the partially hydrolysed derivative so obtained is then established as follows :—

(i) The compound is methylated with CH_2N_2 when the free hydroxyl groups generated after the hydrolysis are methylated.

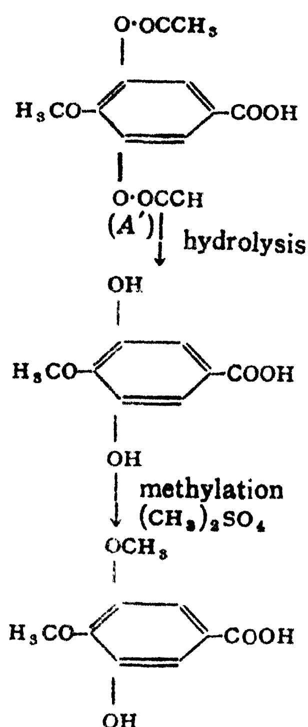
(ii) The acetyl groups are then eliminated by controlled hydrolysis, which does not affect the—OCH_3 linkage.

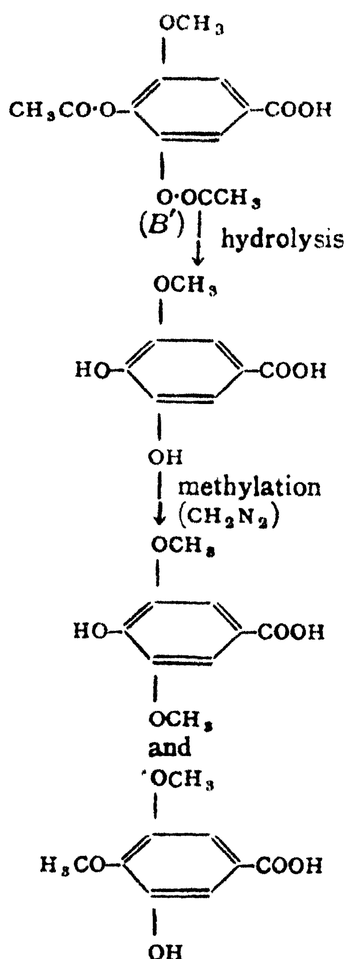
(iii) The methyl ether, thus formed, is identified by suitable analytical methods.

The application of the foregoing method may be illustrated in the case of gallic acid :—



On methylation with diazo-methane, *A* and *B* would give *A′* and *B′* respectively. Their structures are then established by a study of a series of reactions as indicated below.

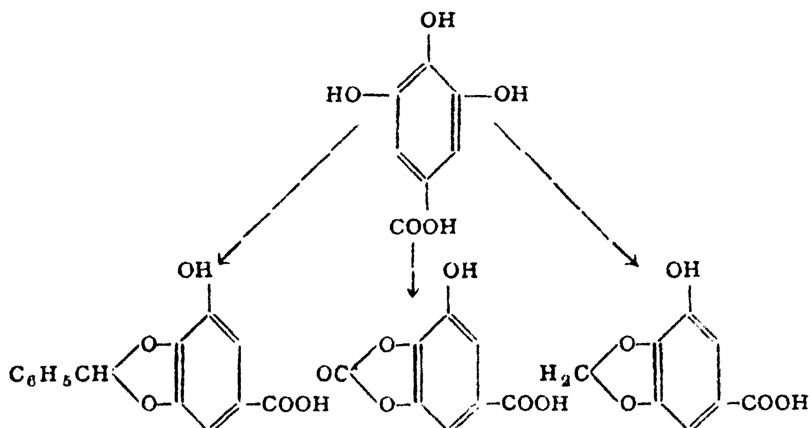




Thus, at the end of the series of reactions, *A* would give only *one* dimethyl derivative, while a mixture of *two* isomeric dimethyl ether derivatives would result from *B*.

Second method :—This method was also used by Fischer, in the case of poly-hydroxy acids with two *OH* groups in ortho positions. The acid was condensed with $COCl_2$ or $C_6H_5{\cdot}CHO$ or CH_2I_2, when an either of the methylene type was formed.

The free *OH* groups can be regenerated after the condensation, under conditions which do not attack the *CO·O*-linking.



(*b*) The condensation of a molecule of the fully acetylated hydroxy acid with a molecule of the partially acetylated hydroxy acid. This is achieved by the interaction of the chloride of the fully acetylated acid with the phenolic group of the partially acetylated molecule in the presence of alkali like *NaOH* or dimetylamine in acetone solution. The acid chloride is prepared readily by the action of PCl_5 on the fully acetylated molecule.

(*c*) The elimination of the acetoxy groups by hydrolysis in the cold. NH_3 is often used in presence of pyridine. Na_2CO_3 solution can also be employed with advantage.

The foregoing methods may be illustrated by following a synthesis of a typical depside, *viz.* *m*-digallic acid, from gallic acid (see p. 129). The *m*-digallic acid is a *di-depside* obtained from gallic acid. This unit *esterifies* the five hydroxyl groups of a glucose molecule to give a synthetic tannin, *viz.* penta-(*m*-digalloyl) glucose.

General Properties of the Depsides :—All depsides are readily decomposed by excess of alkali at the ordinary temperature. The di-depsides of gallic, proto-catechuic and β–resorcylic acids precipitate dilute solution of glue. They also give a precipitate with quinine acetate even at high dilutions. In this property, the resemble closely the natural tannins, but differ from the parent phenolic acids. Like the parent acids, they however, give colour reactions with $FeCl_3$, and are acidic in reaction and can also be readily methylated by diazomethane. However, they differ from the natural tanniss in

two respects: (i) They are not glucosides (ii) They carry a free–COOH group in their molecule.

SYNTHETIC PRODUCTS OF HIGH MOLECULAR WEIGHT:—The foregoing synthetic methods have been applied to the building of compounds with a very high molecular weight. The molecular weight of penta-methyl-*m*-digalloyl glucose is 180. Fischer has also synthesised the penta-(tri-benzoyl-galloyl)-*p*-iodo-phenylmaltosazone. This is a molecule of gigantic dimensions with the molecular weight of 4021, which exceeds that of any other synthetic product. In E. Fischer's own words, "With this number, the compound stands at the head of all organic substances of known structure and is, in addition accessible by complete synthesis."

DEPSIDES IN NATURE:—Depides are obtained as products of hydrolysis of the *lichens*, which thus constitute the solitary prolific natural source of the depsides. The most important acids isolated from the lichens are (*a*) orsellinic acid, (*b*) lecanoric acid (*c*) evernic acid, (*d*) gyrophoric acid.

These are together referred to as "moss acids." Their compositions are as follows:—

orsellinic acid, $C_8H_8O_4$,
lecanoric acid, $C_{16}H_{14}O_7$,
evernic acid, $C_{17}H_{16}O_7$,
gyrophoric acid, $C_{24}H_{20}O_{10}$,

The four acids are closely related to one another. Lecanoric acid, evernic acid and gyrophoric acid, on hydrolysis, give orsellinic acid. From this fact, and from their molecular composition, it follows that orsellinic acid is the phenolic acid, out of which the other three are built up.

CONSTITUTION OF ORSELLINIC ACID:—It has the molecular composition $C_8H_8O_4$. It is formed by the hydrolysis of many lichen products. Its structure is based on the following evidence:—

(*a*) On heating, it loses CO_2 and forms orcinol.

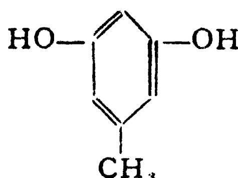


$$C_8H_8O_4 \rightarrow \underset{\text{orcinol}}{C_7H_8O_2} + CO_2$$

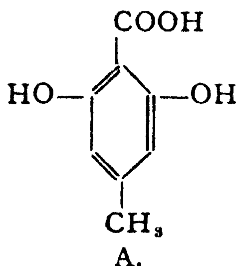
(*b*) It gives a purple-violet colouration with $FeCl_3$ solution. Hence, it is obvious that orsellinic acid is a carboxyl derivative of

orcinol and the *COOH* and *OH* groups are in ortho-position to each other, as in salicylic acid. The ease of decarboxylation suggests that it is an ortho-hydroxy carboxylic acid.

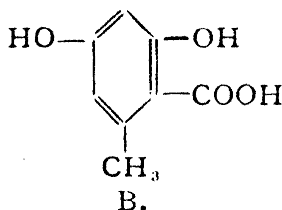
Since orcinol is represented by the following structure :—



Orsellinic acid may be represented by either *A* or B.

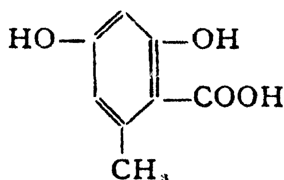


A.



B.

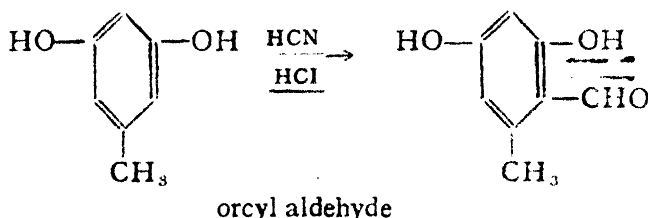
In both of these, the *COOH* and the *OH* groups occupy *ortho* positions. The constitution is then arrived at by a study of its methylation products. Formula *(A)*, being a symmetrical molecule allows for the formation of only *one* mono-methyl ether. Formula *(B)*, on the other hand being unsymmetrical, would yield a mixture of *two* mono-methyl ethers. Experimentally, it has been possible to obtain a mixture of *two* isomeric mono-methyl ethers from orsellinic acid. The constitution of orsellinic acid is hence, represented by formula (*B*).



It is thus, the higher homologue of β-resorcylic acid. The above structure is established by a synthesis.

SYNTHESIS :—It can be readily synthesised from orcinol, to which it is related.

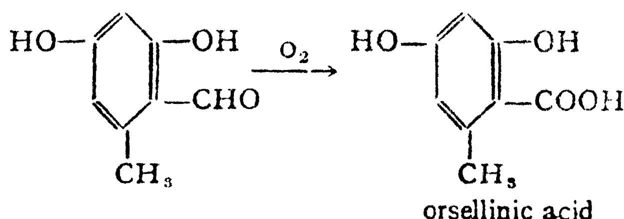
(i) Orcinol is first converted by the Gattermann reaction into the orcyl aldehyde.



orcyl aldehyde

[The orcyl aldehyde on distillation with zinc dust would give o-toluic aldehyde, which would definitely establish the position of *CHO* in the molecule.]

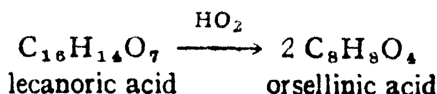
(ii) The orcyl aldehyde on oxidation with $KMnO_4$ in acetone solution gives orsellinic acid.



orsellinic acid

This synthesis finally confirms the structure. It is a crystalline compound which melts at 176° with decomposition.

LECANORIC ACID :—It occurs in many lichens, especially the lecanoraf roccella and variola species. These contain an ester *erythrin* which on hydrolysis, gives *lecanoric acid.* Its molecular, composition is $C_{16}H_{14}O_7$. Its structure is based on its relation to orsellinic acid. Thus, on hydrolysis, it gives two molecules of orsellinic acid.



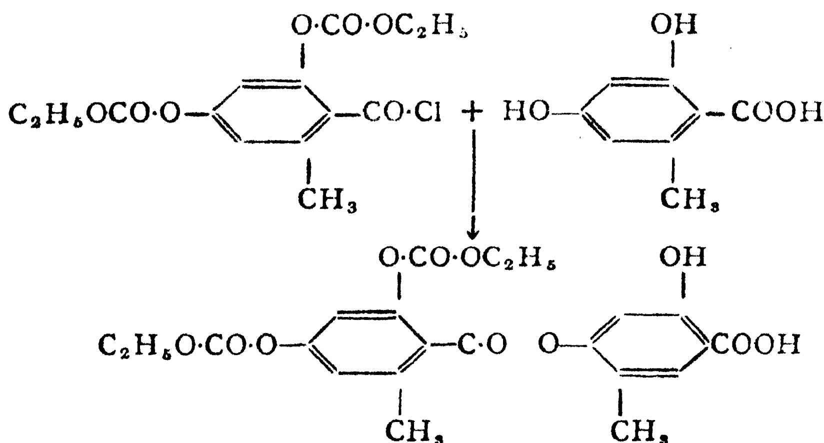
$$C_{16}H_{14}O_7 \xrightarrow{HO_2} 2\,C_8H_8O_4$$

lecanoric acid — orsellinic acid

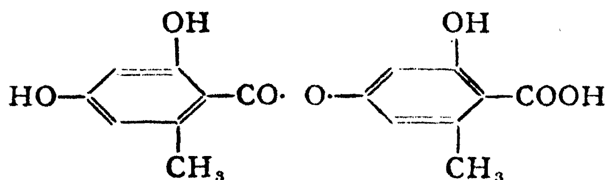
Further, methylation of leanoric acid and subsequent hydrolysis of the trimethyl lecanoric acid, yields *o-p*-dimethyl ether of orsellinic acid and *o*-methyl ether of orsellinic acid, in equal amounts. These results indicate that lecanoric acid is a *para*-di-depside of orsellinic

acid. The above constitution was established by Fischer by a complete synthesis.

SYNTHESIS OF LECANORIC ACID :—The dicarbo-ethoxy orsellinic acid chloride obtained by standard methods used in such a depside synthesis, is condensed with orsellinic acid in the presence of *NaOH*, in the cold.



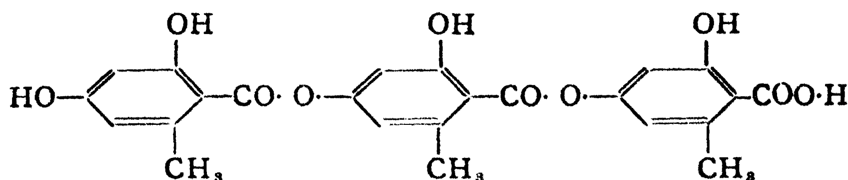
This case, a para condensation takes place, because the para OH is more reactive than the ortho-hydroxyl group ; on careful hydrolysis, the corresponding di-depside, identical with the natural product is obtained. Hence lecanoric acid is :



It melts with decomposition at 166°. It is sparingly soluble in water and is the *para*-di-depside of orsellinic acid.

Gyro-phoric was supposed by Fischer to be an isomer of lecanoric acid. The recent researches of Asahina have proved that it is a tri-depside built up of three molecules of orsellinic acid. It has the molecular composition $C_{24}H_2O_{10}$ and on acid hydrolysis,

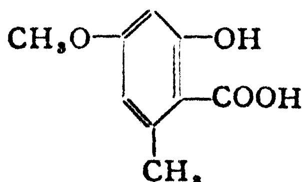
gives three molecules of orsellinic acid. It has been assigned a *para*-depside structure:



Its melting-point is 220°. It has been synthesised.

Evernic Acid:—It occurs in lichens especially of the kind of *evernia*. Its molecular composition is $C_{17}H_{16}O_7$. A comparision of its composition with that of lecanoric acid indicates that it is a methyl ether derivative or a higher homologue. The conclusion regarding its exact constitution is reached by the following experimental evidence. On hydrolysis, it gives (i) orsellinic acid and (ii) everninic acid (*cf.* lecanoric acid gives 2 molecules of orsellinic acid). Everninic acid has the molecular composition $C_9H_{10}O_4$. On heating with concentrated HI, it gives CH_3I and orsellinic acid. Finally it is obtained from orsellinic acid by the action of CH_2N_2. These results indicate that everninic acid is the monomethyl ether of orsellinic acid.

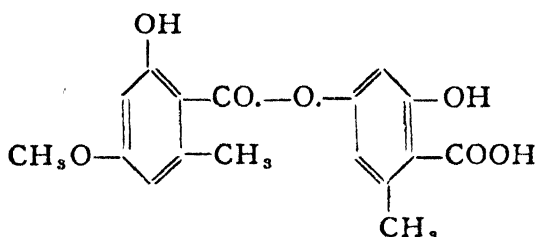
Further, it has been proved that methylation with CH_2N_2 takes place more readily in the *para* position to the *COOH* group, than in the ortho. A free *OH* group in ortho-position to *COOH* in the molecule, is indicated by the colour reaction with $FeCl_3$ and also by the ease with which the molecule suffers decarboxylation on heating. Hence, everninic acid has the formula.



It has been synthesised by Hoesch, starting from orcyl aldehyde.

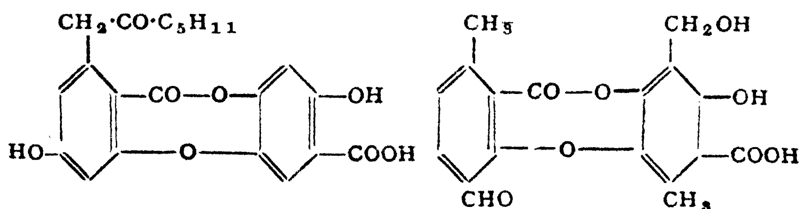
Now, evernic acid is the di-depside obtained from orsellinic acid and everninice acid. The mode of linking of the two units is then

established as follows : Fischer found that lecanoric acid and evernic acid on complete methylation give identical products. Lecanoric acid is a *para*-di-depside; hence, evernic acid must also be a *para*-di-depside. Further, there is no hydroxyl group, in the *para* position in the everninic acid residue. It is probable, therefore that this molecule furnishes the carboxyl group, which condenses with the *para—OH* of the orsellinic acid residue. Hence, the structure for evernic acid is:—

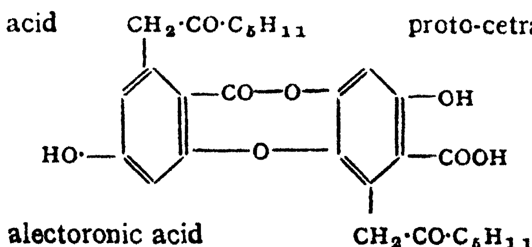


It is thus mono-methyl ether of lecanoric acid. The above structure is confirmed by a synthesis.

DEPSIDONES :—Many lichens contain depside-like compounds but which differ from the depsides in not being decomposed by alkali into their constituent hydroxy acids. They contain an ether linking (*C—O—C*) in addition to the depside linking (*CO—O—*). They are called depsidones by Asahina. Some of the common depsidones are :—

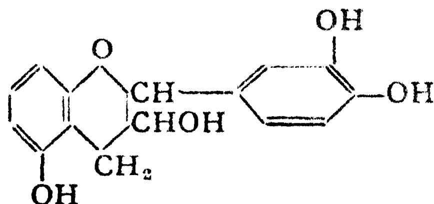


physodic acid proto-cetraric acid



alectoronic acid

CATECHINS :—They are the parent substances of many natural tannins *e.g.* phloba-tannin or tannin red. They are colourless crystal line compounds. Structurally, they have been shown by Freudenberg to be related to the flavonols. *l*-Epicatechin from acacia catechu has been assigned the following contitution :—



l-epi-catechin

Thus, it contains the reduced flavonol system. This is further confirmed by the conversion of cyanidin into *dl*-epicatechin by the action of hydrogen in presence of platinum in alcohol, Similarly, *l*-epicatechin can be changed into cyanidin by an indirect method.

Some other catechins known, are the *d*-catechin from *Uncaria gambir* and tea-catechin II or gallo-catechin from green tea. The latter is related to delphinidin in the same way as epi-catechin is related to cyanidin.

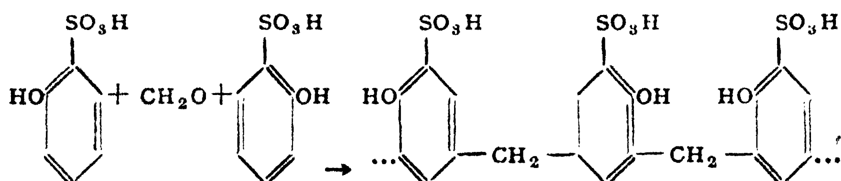
SYNTANS

The syntans represent the modern synthetic materials, that can be used for the purposes of tanning, in place of the natural tanning materials. The natural tannins have been established to be phenolic in nature ; hence it is obvious that phenolic compounds, should form the starting materials for such synthesis.

Schiff, Weinschenk and Neaf carried out a large amount of work which involved the condensation of phenol-suphonih acids, naphthol etc., with formaldehyde in presence of con. H_2SO_4 or oleum. The modern syntans belong to one of the following general types :

(*a*) Ar—CH_2—Ar. ; Ar = a phenol sulphonic acid residue ; phenol sulphonic acids, cresol-sulphonic acids are used in the manufacture of this class of syntans ; the phenol-sulphonid acid, formaldehyde and con. H_2SO_4 are condensed together under mild condition; the mixture is heated together at 100—120° for some time ;sometimes

heating is not at all necessary as the addition of the reactant produces enough heat; the mixture is then cooled and treated with 98% H_2SO In another method, the phenolic compounds and con. H_2SO_4 are added together, the mixture cooled and diluted with water and finally treated with formaldehyde. the temperature not being allowed to rise above 30°. The product obtained is a colourless, viscous mass soluble in water. The probable reactions involved are :—



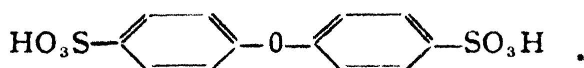
Instead of C_6H_5OH, and the corresponding sulphonic acid, the higher phenols or their sulphonic acid derivatives may be used; also in place of formaldehyde, other aldehydes and ketones have been used. However, the products thus obtained are found to be inferior as tanning materials.

Neradol D is one of the most successful important syntans. It was first obtained by Stiasny; it is now prepared by sulphonating the cresol and condensing the sulphonic acids formed with formaldehyde; or cresol is first condensed with formaldehyde and subsequently sulphonated; the condensation is effected by dilute acid. The use of regulated quantity of alkali has been recommended. Neradol D is in the form of a Na-salt and forms a viscous liquid soluble in cold water. It smells slightly of phenol and is acidic to methyl orange. It is completely precipitated by gelatin; with bromine water it gives no precipitate; with $FeCl_3$ a deep-blue coloration is produced; thus in all these reactions the synthetic tannins closely resemble the natural tannins.

Neradol D is often used in conjunction with vegetable tannins; under these conditions, it is found to possess a great practical advantage; the phlobaphenes present in the vegetable tannins to which the tanning materials owe their colour are hydrolysed by Neradol D. This increases the efficiency of tanning (the hydrolysis leads to production of more tanning material) and also helps to

increase the colour of the tanned product on account of a greater absorption and fixation of the phlobatannins formed.

(*b*) Ar—O—Ar; Ar = a phenol—sulphonic acid residue. Such compounds are obtained by the condensation of the phenol sulphonic acids without the aid of any aldehyde. A good number of these are obtained by condensing the naphthalene sulphonic acids by heat alone at 130° under reduced pressure. Structurally they are sulphonated aromatic ethers.



Some syntans are also known to be produced when phenol sulphonic acids are heated with $POCl_3$ or sulphur chloride as condensing agents.

CHAPTER III

POLYMETHYLENES

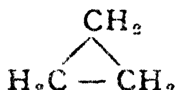
INTRODUCTION—The polymethylenes are cyclic hydrocarbons classed with the *carbo-cyclic* compounds, which are sub-divided into—(*i*) aromatic and (*ii*) alicyclic compounds or polymethylenes. The polymethylenes are found in the petroleum of the asphalt base. The Galician and Caucasian mineral oils contain a considerable proportion of these compounds. They are termed "naphthenes". The naphthenes are the alkyl derivatives of cyclopentane and of cyclohexane, both of which are also present in the petroleum. Fourteen of these have been isolated in a pure form ; they are the methyl and ethyl derivatives.

The six-membered ring system is the most important and is the most frequently encountered with, in nature. Many of these compounds have been synthesised in the laboratory. The terpenes and camphors—the constituents of the essential oils from citrus fruits, leaves and flowers—are derived from the *p*-menthane system which is related to the polymethylenes. The sterols, bile acids etc. also contain condensed polymethylene systems.

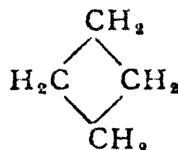
GENERAL COMPOSITION AND BEHAVIOUR—The polymethylenes are hydrocarbons with the empirical composition $(CH_2)n$ where $n=3, 4, 5, 6, 7, 8$, or 9. They are thus *isomeric* with the olefins. However, they do not exhibit unsaturation like the latter and their reactions and behaviour in general and the mode of their preparation point to a cyclic, closed ring structure. The addition reaction of the olefins with reagents like halogens, hypohalogen acids, halogen acids, and potassium permanganate are not given by them. The lower members react with the halogens in a way apparently similar to that of ethylene. But the higher members usually undergo substitution reactions with these reagents. They resemble more closely the saturated paraffin hydrocarbons. They are thus more aliphatic in character. They contain two atoms of hydrogen less than the corresponding paraffin, the missing hydrogen atoms being removed in ring formation; in the case of the alkenes (ethylenes), the missing hydrogen atoms are removed to produce the double bond.

They also give rise to derived functions. alcohols, aldehydes ketones, acids and amines, which are obtained by the replacement of the hydrogen atoms by the corresponding functional group. Unsaturated polymethylenes containing one or more double bonds or with a triple bond are also known.

NOMENCLATURE :—The empirical composition of these compounds reveals that they are built up of CH_2 *i. e.* methylene groups. Hence, their class-name is *poly* (many) *methylenes*. A compound containing three carbon atoms is called tri-methylene, one containing four carbon atoms tetramethylene and so on. They are also referred to as *cyclo-paraffins* or cyclo-alkanes, on account of their ring structure (cyclo) and their close similarity to the paraffins. The polymethylene is then named by affixing the term *cyclo* to the name of the paraffin containing the same number of carbon atoms. Thus, we have :



tri-methylene or cyclo-propane



tetra-methylene or cyclo-butane

Another class-name suggested by Bamberger for these compounds is "alicyclic compounds." This connotes that they are both aliphatic (ali) and cyclic in structure and their general chemical behaviour. The name of a cyclic alcohol, acid or ketone is derived from that of the cyclic paraffin ; the positions of the functional groups in the ring are further indicated by a number. The unsaturated cycloparaffins are named in relation to the corresponding saturated system.

Thus, we have :—

C_6H_{12}	cyclo-hexane
C_6H_{10}	cyclo-hexene
C_6H_8	cyclo-hexadiene
C_6H_6	benzene (organic)

GENERAL METHODS OF SYNTHESIS :—A number of methods have been developed by various chemists, like Perkin, Wislicenus, Ruzicka and Ziegier for the synthesis of different alicyclic ring systems. They can be conveniently divided into two groups :

(*i*) Those which lead to the synthesis of six-membered ring systems which are essentially related to aromatic compounds, and,

(*ii*) Those which lead to the synthesis of ring systems other than the six-membered for which numerous synthetic methods based on different principles are available.

THE SIX-MEMBERED RING COMPOUNDS :—They are usually obtained from the aromatic systems by catalytic hydrogenation. Hence the six-membered polymethylenes are called hydro-aromatic compounds. Hydrogenation is carried out in one of the following ways :—

(*a*) By Sabatier and Senderens method, in the vapour phase at 200°–400°C. (reduced Cu or Ni as catalyst).

(*b*) In the liquid phase at 100°–200°C. with Ni under high pressure 50–200 atms; this process is suitable to most of the aromatic compounds (Ipatieff's method).

(c) At ordinary temperature and pressure; the catalysts used are *Pt*-black (Willstatter) or colloidal *Pt* or *Pd*, or PtO_2 in alcohol, acetic acid (Adams).

In this way, benzene has been converted into cyclo-hexane and phenol into cyclo-hexanol (sextol),



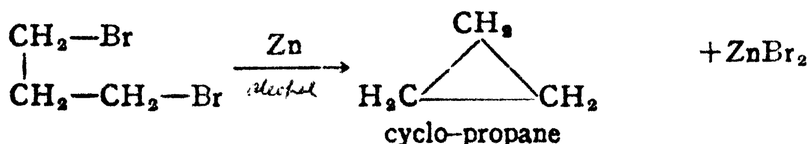
$$C_6H_6 + 6H \longrightarrow C_6H_{12}$$
$$C_6H_5OH + 6H \longrightarrow C_6H_{11}OH$$

OTHER RING COMPOUNDS :—For the synthesis of other ring systems, three main types of methods are generally used. They include : (*a*) ring closure methods—here the ordinary synthetic methods are applied in such a way that instead of the formation of large molecules, the reactants give rise to ring or closed systems. Thus, while the condensation of ethyl acetate gives rise to acetoacetic ester, the condensation of the diesters of the dibasic acids, like adipic, pimelic etc. yields five and six-membered ring systems respectively, by intramolecular condensation; (*b*) ring expansion methods and (*c*) ring contraction methods. These methods involve *intra-molecular* changes, which lead to a change in the size of the ring. These re-arrangements resulting in the formation of a larger or a smaller ring in the alicyclic series, may be compared to similar re-arrangement reactions in the aliphatic series which lead to a shift of carbon-carbon double linkage.

RING CLOSURE METHODS :—These cover a very wide range. Starting from suitable open chain compounds, it is possible to synthe-

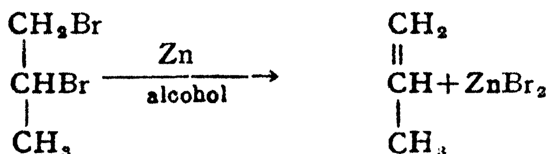
sise rings with varying number of carbon atoms and with different functional groups. A number of important practical methods have been developed to synthesise: (*a*) hydrocarbons, (*b*) alcohlos, (*c*) ketones, and (*d*) acids, all belonging to this series.

(*a*) HYDROCARBONS (Cyclo-paraffins): An—α—ω-di-halogen derivative is treated with sodium in an inert solvent like ether or benzene. This is the Freund's reaction. A more convenient condensing reagent is zinc and alcohol. When nitro-groups are present, Cu powder gives better results.



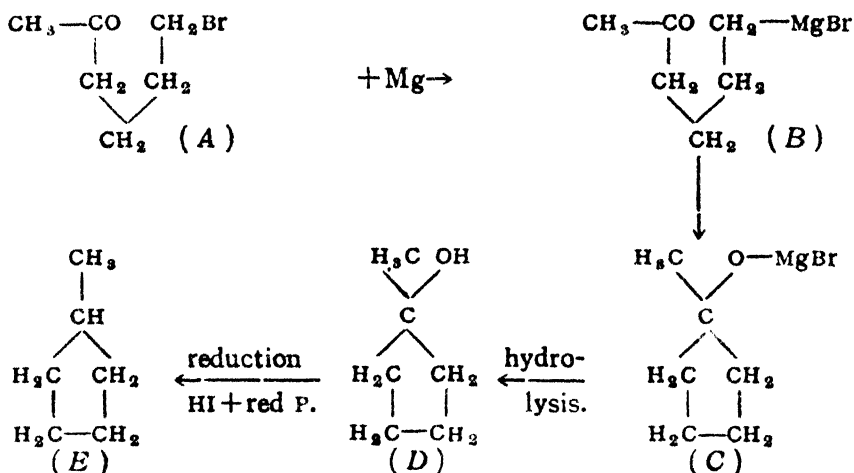
This method is limited in its application. It can be employed to synthesise the lower members only. Even with five or six-membered rings, the yields are extremely poor, because of many side-reactions. However, good yields are obtained with the three-membered ring systems. The method fails entirely in the case of four-membered ring systems.

If the halogen atoms are on adjacent carbon atoms, an olefin is the sole product, under the same experimental conditions.



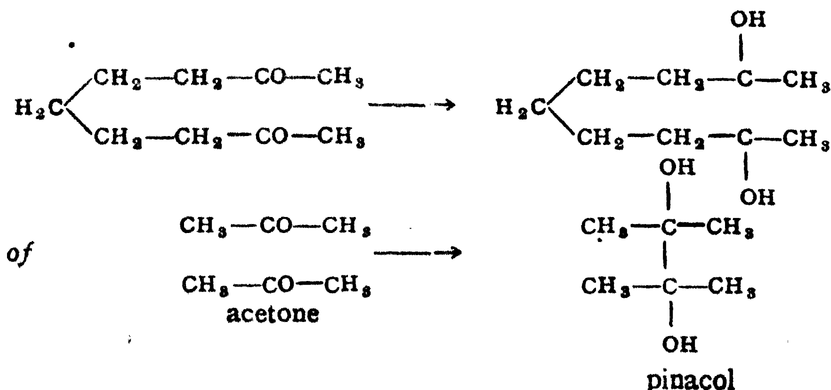
The formation of an olefin takes place more easily than the formation of a three-membered ring system. The latter system in turn, is formed more easily than a four-membered system. An olefin is also obtained by boiling the α-β-dihalogen compound with KI in alcohol. The di-iodo-derivative is first formed, which subsequently suffers de-iodination to yield the olefin.

(*b*) CYCLIC ALCOHOLS (Hydroxy polymethylenes):—They are obtained by the action of magnesium on the halogen derivatives of open chain ketones. This is an extended application of the Grignard reaction.



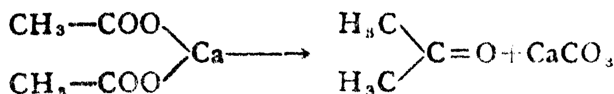
Magnesium reacts with the—CH_2Br—group to form a compound (*B*) of the type of a Grignard reagent (*cf.* CH_5MgBr). Now the Grignard reagent is known to react readily with *ketonic* function to give an alcohol. In the present case, the carbonyl group forms a part of the Grignard reagent itself. Hence, an *intra-molecular* reaction takes place to give (*C*). On hydrolysis with dilute acids, the corresponding cyclic alcohol (*D*) is formed. The corresponding polymethylene (*E*) is then obtained by reduction of the alcohol with concentrated hydriodic acid in presence of red phosphorus. A recent modification is to employ a mixture of KI, red P and H_3PO_4 (90%); the yields of the polymethylene are excellent.

(*c*) CYCLIC GLYCOL (Dihydroxy derivatives) :—This synthesis involves the reduction of a suitable diketone by magnesium amalgam. This is analogous to a pinacol formation.

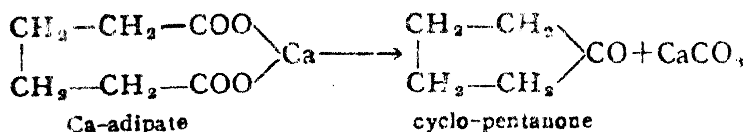


The glycol may then be reduced to the corresponding polymethylene.

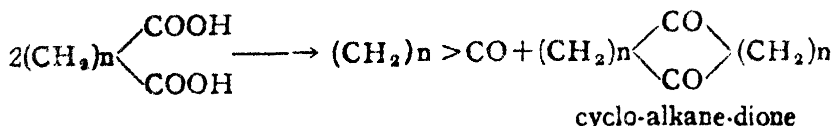
(*d*) CYCLIC KETONES (Wislicenus' method) :—This consists in the distillation of the calcium salt of a dibasic acid. This is similar in principle to the formation of acetone from calcium acetate.



Similarly, the calcium salt of adipic acid gives cyclopentanone.



This is probably the oldest and most general reaction used in the synthesis of polymethylene compounds. However, it suffers from some practical limitations. It is not applicable to the synthesis of a three-membered ring. Ca-succinate when distilled gives a six-membered cyclic diketone, instead of a three-membered ring. The temperature conditions involved are very high and hence, the reaction is drastic and the yields, are not quantitative. A troublesome by-product is the cyclo-alkane-dione :—



The behaviour of the dibasic acids is formulated by the Blanc's rule : Dibasic acids containing 6 or 7 carbon atoms when heated with $(CH_3CO)_2O$ and distilled at 300° give cyclic ketones, while those containing 4 or 5 carbon atoms yield cyclic anhydrides This rule has been of great practical importance in the determination of the size of a ring in the steroid molecule. However the Blanc's rule is not reliable in those cases in which the two COOH groups are attached to different rings.

The exact mechanism of thermal decomposition involved in this method is still unknown. The yield of the cyclic ketone obtained depends on the salt (metal) used, and on the number of carbon atoms in the ring.

Acid	Calcium salt	Thorium salt
Glutaric acid	0 per cent	0 per cent
Adipic acid	45 per cent	15 per cent
Pimelic acid	40-50 per cent	70 per cent
Suberic acid	35 per cent	50 per cent
Azelaic acid	5 per cent	20 per cent

It is now postulated that cyclisation is based on two factors; (*a*) the distance factor and (*b*) the strain factor.

In recent years, this method has been modified by Ruzicka who uses the thorium and yttrium salts mixed with copper filings; the distillation is carried out in vacuo. The yield of the cyclic ketone is also much improved.

The cyclic ketone $(CH_2)n > = O$ and the cyclic diketones $(CH_2)n\begin{matrix} CO \\ CO \end{matrix}(CH_2)n$ can then be reduced by amalgamated zinc and hydrochloric acid (Clemmensen's method) to the corresponding hydrocarbon. Ruzicka, using this method, has prepared cyclo-paraffins containing from 8 to 34 carbon atoms.

The Clemmensen's method is a simple and elegant method. Recently, Martin has found that better results are obtained by adding a layer of toluene to the reaction mixture. Vigorous boiling is maintained to keep the layers well mixed; a longer period of refluxing is also required. But this is compensated by the formation of a much purer product. The poly-molecular side-reactions are completely suppressed.

A second method, known as Wolff-Kishner method, is an excellent method for converting a CO group into—CH_2. It depends on the catalytic decomposition of a hydrazone of an aldehyde or ketone, with $NaOCH_3$ or $NaOC_2H_5$ or with solid KOH.



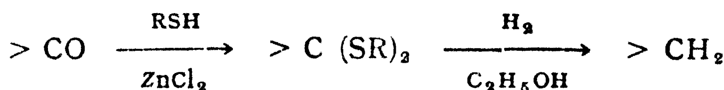
$$>C = N - NH_2 \longrightarrow >CH_2 + N_2$$

With $NaOCH_3$, the decomposition is carried out in a sealed tube at 160°. With solid KOH, the temperature range required is 190—200°. This is a very valuable complementary tool to the Clemmensen's method. The latter cannot be used to reduce pyrrole, and furane derivatives, as these are sensitive to acid. Further the Wolff-Kishner method succeeds with compounds of high molecular weight, where the Clemmensen's method fails because of the insolubility of the compounds. The W-K reaction is remarkably

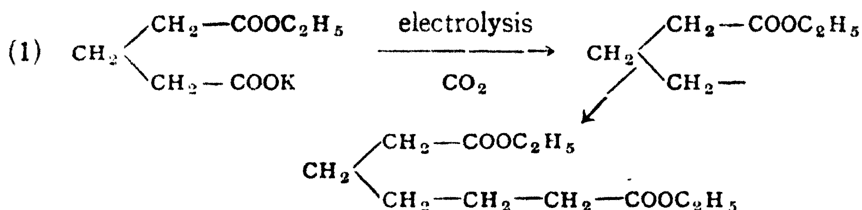
insensitive to steric hindrance. Several highly substituted ketonic compounds have been reduced.

Huang–Minlon has modified the method so that the reduction can be effected on a large scale, at atmospheric pressure and with efficiency and economy. The carbonyl compound is refluxed in a high boiling (245°) solvent like diethylene glycol, with aqueous $NH_2—NH_2$ and NaOH. Hydrazone is first formed; the temperature is then gradually raised to 200°, at which the hydrazone decomposes. The reduction is complete within three or four hours.

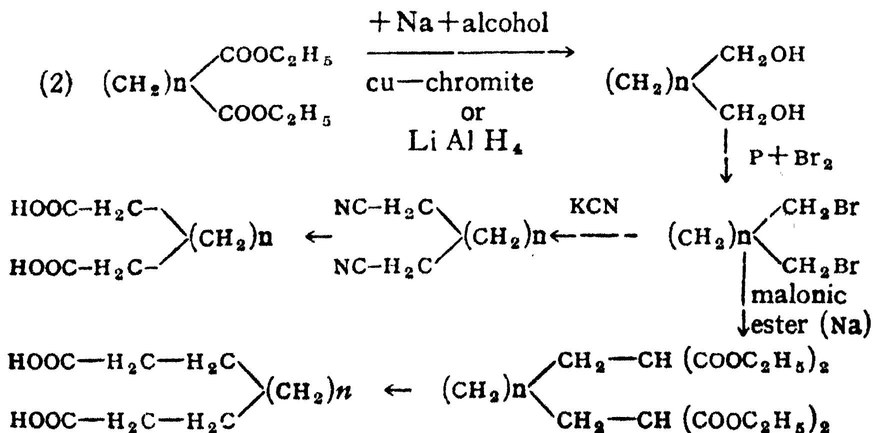
A promising recent method for the reduction of the carbonyl compounds consists in the hydrogenolysis of a dialkyl-thio-acetal derivative of the ketone or aldehyde, with Raney Ni.



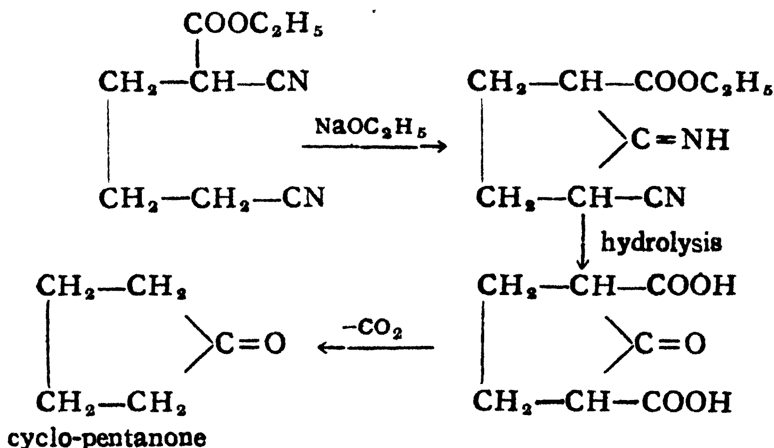
The dicarboxylic acids required in the Ruzicka's method are obtained by one of the following methods :—



The free radical $CH_2\langle^{CH_2—COOC_2H_5}_{CH_2—}$ is first formed, which then condenses with itself. The length of the carbon chain is almost doubled.



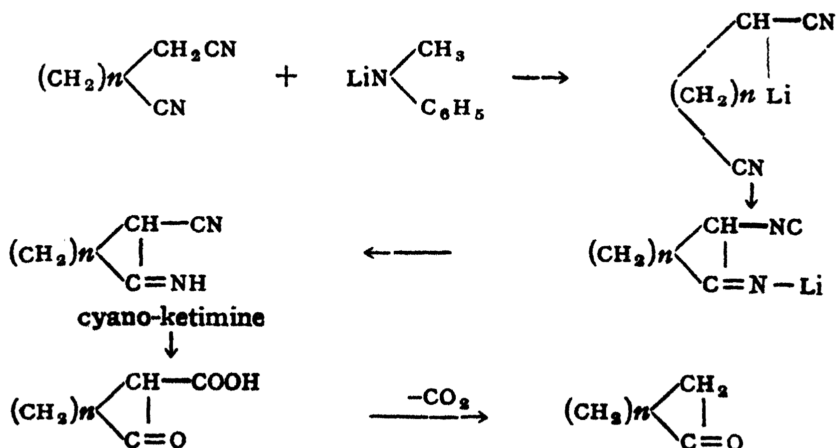
There is still another method due to Thorpe which leads to the synthesis of cyclic ketones. The di-nitriles are made to undergo internal condensation in the presence of sodium ethoxide.



cyclo-pentanone

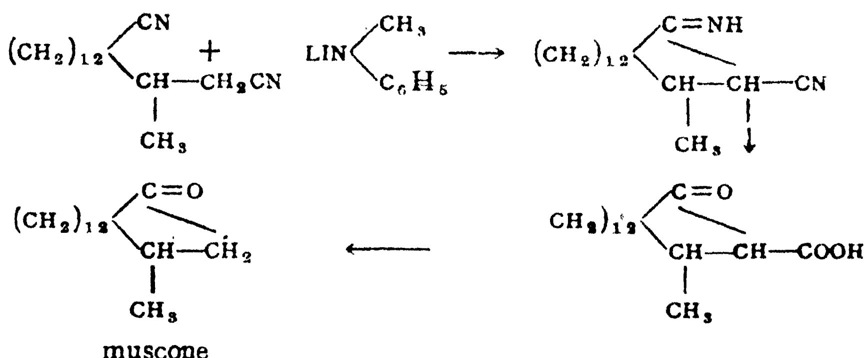
The above method has been modified and extended by Ziegler.

ZIEGLERS' METHOD:—It consists in the action of tertiary metallic alkylamines on *n*-aliphatic di-nitriles: cynoketimines are first formed in good yield which are subsequently hydrolysed to cyclic ketones.



The reaction is carried out at high dilution when *intra*-molecular condensation is favoured, as opposed to *inter* molecular combination.

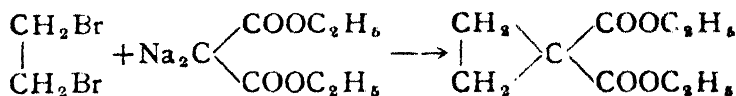
The yield of the ketone is 40 per cent of the theoretical. This is said to be one of the best methods, so far available for the synthesis of large rings. This method has been successfully used for the synthesis of muscone—the constituent of musk.



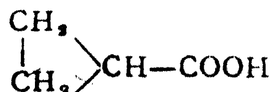
Cyclo-penta-decanone $(CH_2)_{12}\left\langle\begin{matrix} CH_2 \\ CH_2 \end{matrix}\right\rangle C=O$, is now manufactured and sold under the name of 'exaltone' as a substitute for muscone. Muscone is 2-methyl exaltone.

(*e*) Cyclic Carboxy-Derivatives (Perkin's method) : In this method, the di-halogen derivative of the paraffin is treated with the sodium derivative of ethyl malonate or of aceto-acetic ester or of any other 1-3 diketone. In this way, ring systems containing three, four, five and six carbon atoms are synthesised.

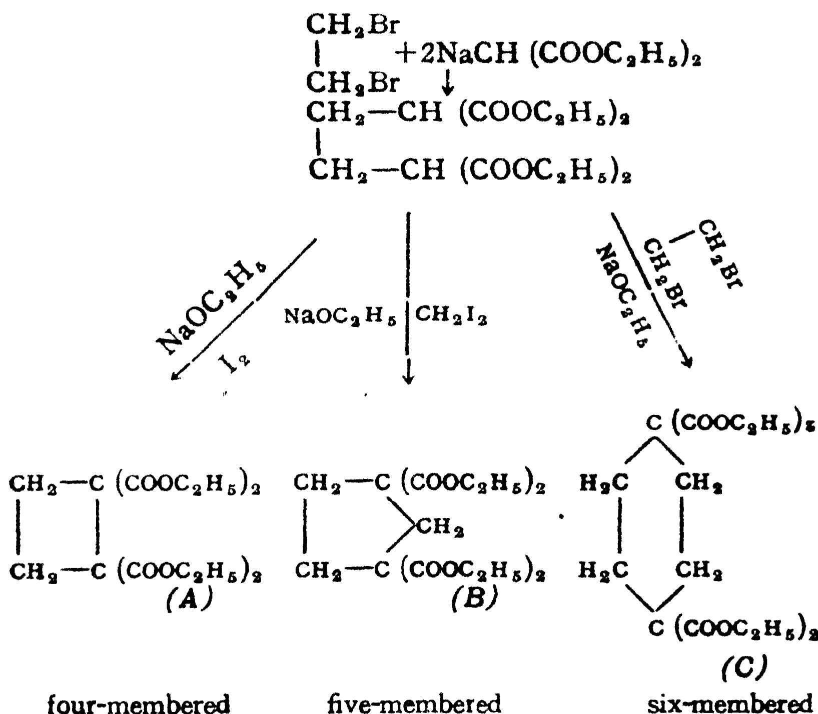
(*i*) Synthesis of three-membered rings :



which on alkaline hydrolysis and subsequent decarboxylation by heating with a mineral acid at 100°C gives:—



(*ii*) Synthesis of four, five and six- membered rings :—



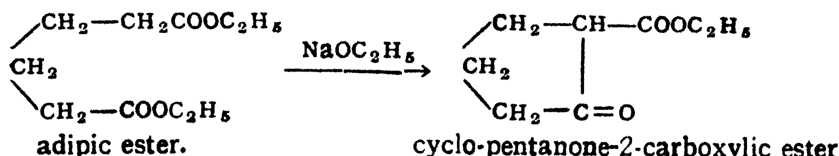
Similarly instead of the malonic ester or acetoacetic ester any other 1, 3–diketone can be used; when acetoacetic ester is used cyclic methyl ketones will be formed.

Thus, this is a method of very wide variation and extension. Rings containing 3, 4, 5, 6, 7 or 8 carbon atoms have been obtained by this method. The yields are in the following order :—

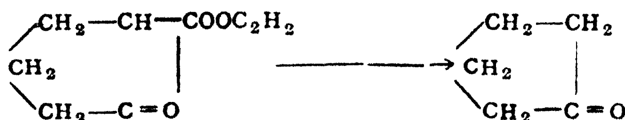
$$C_5 > C_6 > C_4 > C_3 > C_7$$

With C_5, the yield is almost quantitative.

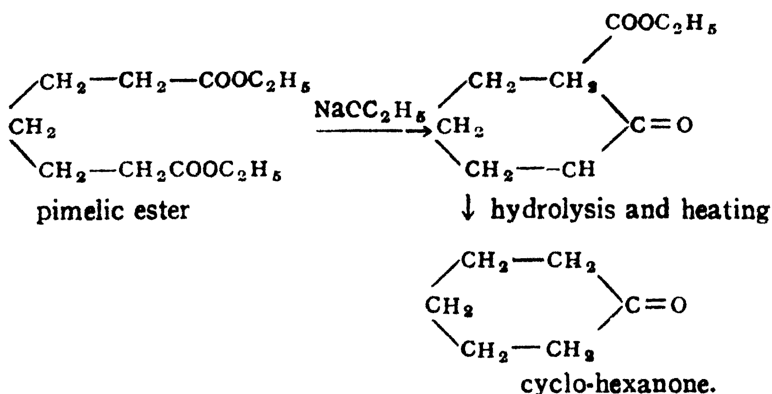
(*f*) KETO–CARBOXYLIC DERIVATIVES :—Dieckmann has developed a method which in principle is an extension of the Claisen's condensation reaction. Under the influence of the mild alkaline condensing agents like sodium ethoxide or sodamide or NaH the esters of dicarboxylic acids containing a suitable number of carbon atoms undergo *intra*–molecular condensation. Glutaric and succinic diesters do not react in the manner to give cyclobutane and cyclopropane derivatives.



By hydrolysis and subsequent decarboxylation, the ketocarboxylic derivative can be converted into a cyclic ketone.



Similarly pimelic ester gives cyclo-hexanone-2 carboxylic ester and then cyclo-hexanone.



The type of condensation involved here is the same as that in the formation of aceto-acetic-ester from ethyl acetate:—

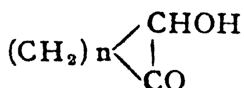


$$2\ CH_3\,COOC_2H_5 \xrightarrow{NaOC_2H_5} CH_3{-}CO.CH_2.COOC_2H_5$$

This synthesis is comparable to Wislicenus' method which also starts from a dibasic acid (the *Ca* or *Ba* salts are used). However, this method is superior to the latter in being less drastic. It is also free from by-products. This reaction has found application in the syntheses of (i) methone (ii) α terpineol, (iii) pinene and (iv) camphor.

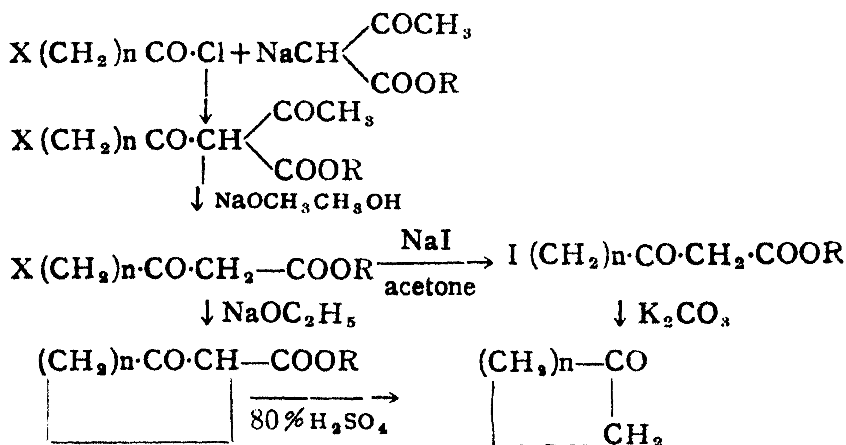
Recently two more methods of synthesising cyclic macromolecules have been developed. One is due to Hansley and the other, to Hunsdiecker.

HANSLEYS' METHOD:—In this method, cyclic acyloins from HOOC. $(CH_2)n$. COOH have been obtained by the action of Na in xylene, on the esters of the dibasic acid. The condensation is effected in an oxygen-free atmosphere. The acyloins formed have the structure:—



The yields are very good; thus it constitutes a very valuable method of synthesising large cyclic molecules.

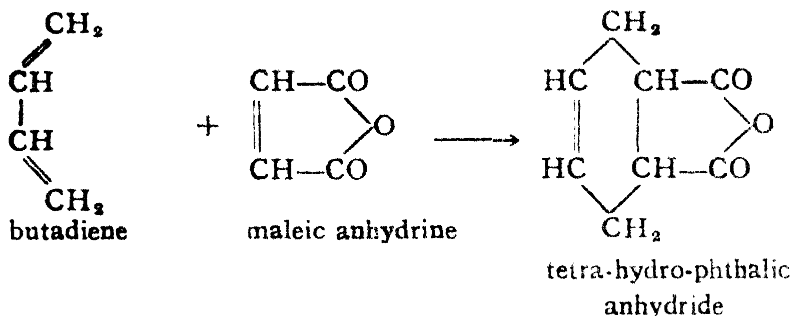
HUNSDIECKER'S METHOD:—Here, the starting material is ω-halogenoacetic esters, whose alkaline salts in dilute solutions yield 40-75% of cyclic keto-carboxylic acids. On decarboxylation, they yield ketones with large single rings.



where X = a halogen.

Many reactions are known in which ring formation takes place as a result of condensation of unsaturated compounds. Some typical cases are: (*a*) the Diels and Alder's reaction. (*b*) intramolecular condensation of cinnamic acid to truxillic acid, (*c*) the Michael condensation and (*d*) Knoevenagel' reaction.

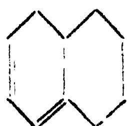
(*a*) DIELS AND ALDER'S REACTION:—This is a reaction of great practical importance. It involves the condensation between a conjugated diene with olefinic carbonyl compounds called the 'dienophils'. Thus we have the condensation between butadiene and maleic anhydride. No catalyst is necessary.



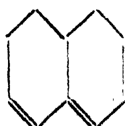
The maleic anhydride condensation is carried out in C_6H_6 or xylene solution. The products are usually crystalline compounds with sharp melting-points and hence the reaction is extensively used to detect the presence of conjugation in an unsaturated molecule. Also the product of the reaction contains invariably a six-membered ring system and therefore the reaction has become a very important tool for the forging of six-membered ring systems.

The reaction can be further extended: (i) in place of butadiene, substituted butadienes or other dienes like cyclopentadiene or furane and the derivatives like vinyl naphthalene may be employed; (ii) the dienophil maleic anhydride may be replaced by other dienophils such as $CH_2=CH-CHO$, *p*-benzoquinone, 1, 4-naphthaquinone etc. In this way, one can synthesise (*a*) benzene, (*b*) naphthalene, (*c*) anthracene and (*d*) phenanthrene systems by the application of the diene synthesis.

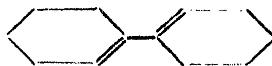
On the analytical side, the reaction has been used to determine whether a conjugated system lies wholly within one ring or otherwise. In the case of the following three types of systems:



A



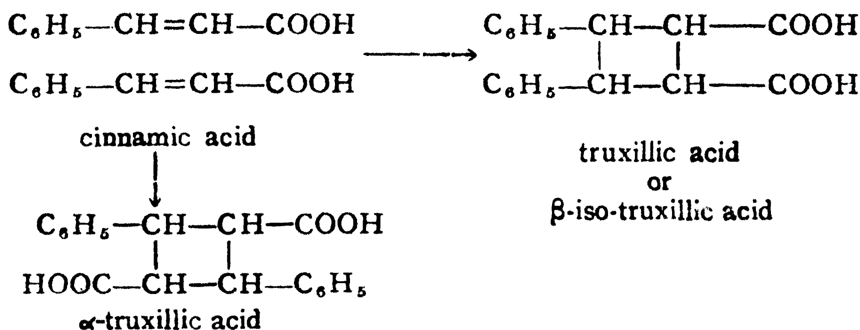
B



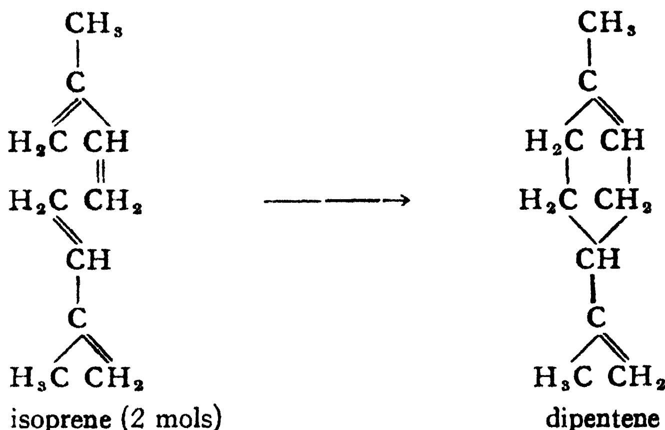
C

the type B, does not form a crystalline adduct at all with maleic anhydride; the type C, does give the normal reaction, while in the case of type A, the adduct formation may take place with difficulty.

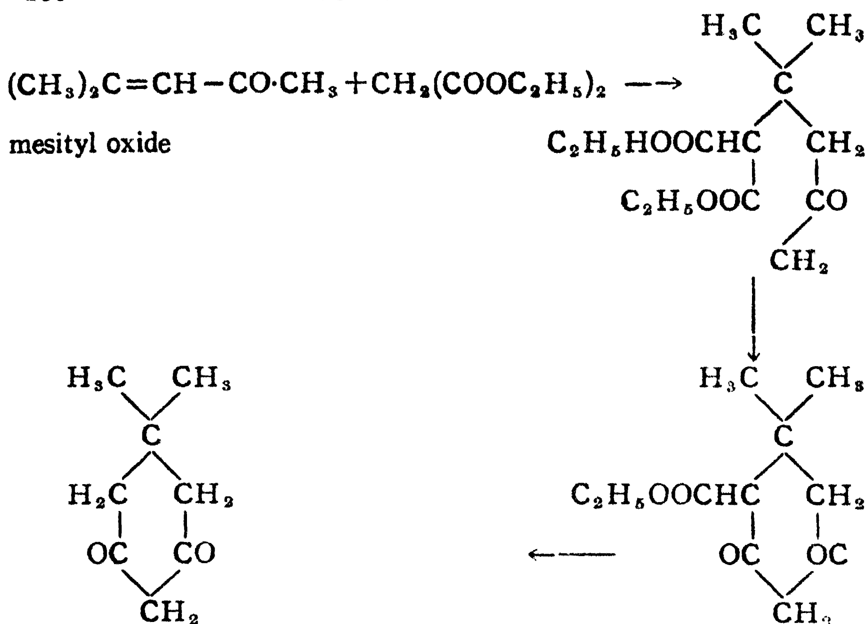
b Condensation of cinnamic acid to truxillic acid, on standing in presence of acids, or on heating : Ring formation is due to intramolecular condensation.



Similarly, isoprene is condensed to dipentene :—



(c) Michael condensation—In this condensation reaction compounds of the general formula R—CH=CH—CO—R′, where $R=CH_3$, C_2H_5 or OC_2H_5 etc. are made to react with compounds containing *reactive methylene* group e.g. $CH_2(COOC_2H_5)_2$, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}COOC_2H_5$ or $CN{\cdot}CH_2COOC_2H_5$ in presence of $NaOC_2H_5$ or tertiary bases like piperidine. It consists of 1-4-addition ; additive compounds are first formed which may further undergo intra-molecular condensation to give cyclic systems. The synthesis of dimethyl-dihydro-resorcinol from mesityl oxide and malonic ester is a typical example of the reaction.

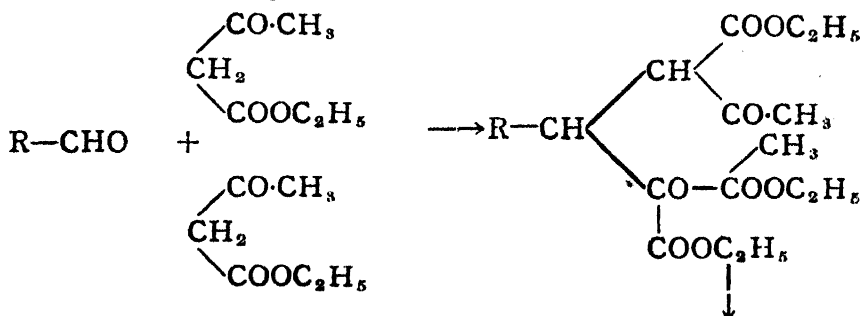


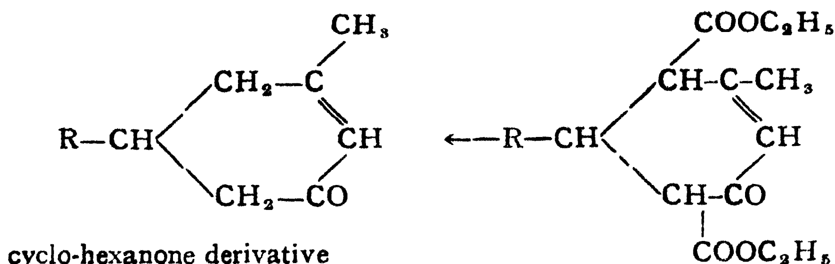
dimethyl-dihydro-resorcinol (dimedon)

Dimedon is a specific reagent for aldehydes. The condensation is effected in aqueous-alcoholic or glacial acetic acid solutions. Usually, the condensation products are crystalline solids with sharp melting-points. Even the lower aliphatic aldehydes *e. g.* formaldehyde give solid crystalline derivatives.

Both the Diels–Alder and the Michæl reactions are cases where CH=CH. system is activated by the proximity of a CO group, and is thus rendered capable of adding on to such molecules as diolefins in the Diels–Alder and to HA reagents in the Michæl reaction.

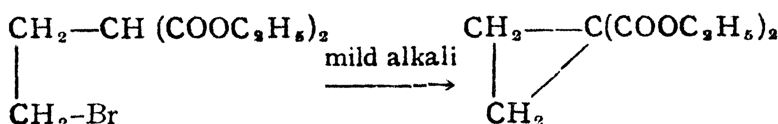
(*d*) Knoevanagel's reaction: condensation of aldehydes and acetoacetic-ester in the presence of secondary or tertiary amine to form six-membered systems.





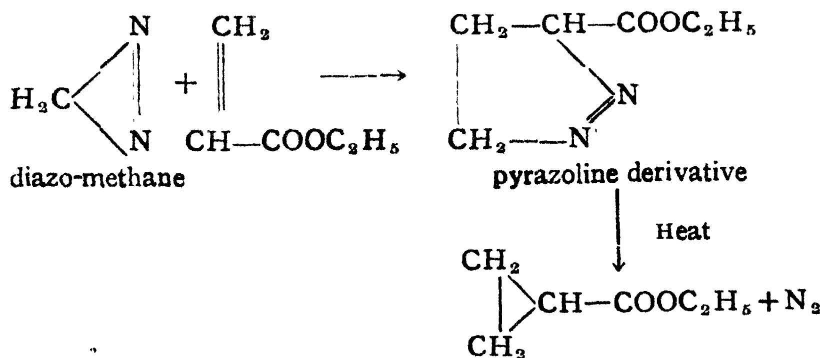
cyclo-hexanone derivative

A few special reactions for synthesising the three-membered rings are; the ring formation may also involve elimination of halogen acid;



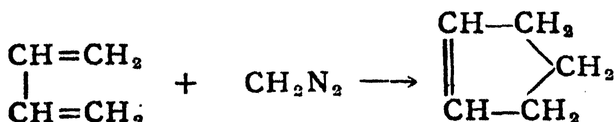
The reaction takes place between the reactive hydrogen atom and halogen atom suitably placed in relation to it.

Another interesting method of synthesising a three-membered ring system is through the pyrazoline derivative (Buchner and Curtius)



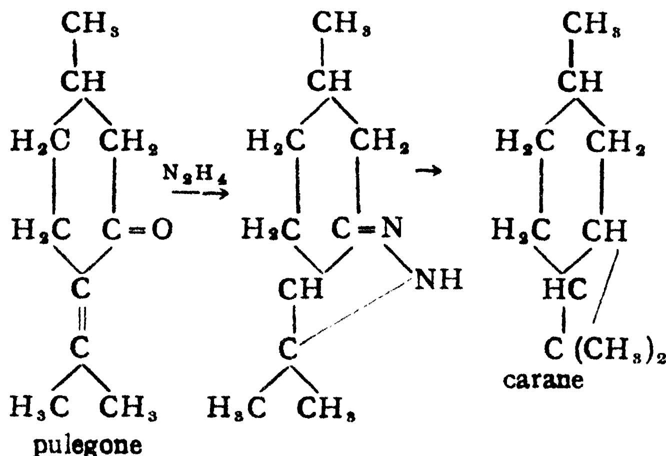
A few reactions involving the use of CH_2N_2, diazo acetic ester of $H_2N—NH_2$ have found some applications in the polymethylene synthesis.

Thus CH_2N_2 may react with butadiene to give cyclo-petene :



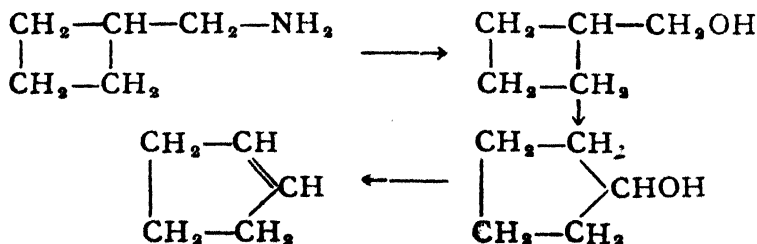
Diazo-acetic ester may be used in place of diazo-methane. Hydrazine also has found some applications. It reacts with unsaturated ketones with the grouping—$CH=CH—CO$, to form pyrazoline derivatives which readily decompose into cyclopropane systems, on heating very strongly.

Kistner's conversion of pulegone into carane, involves the use of $H_2N—NH_2$.



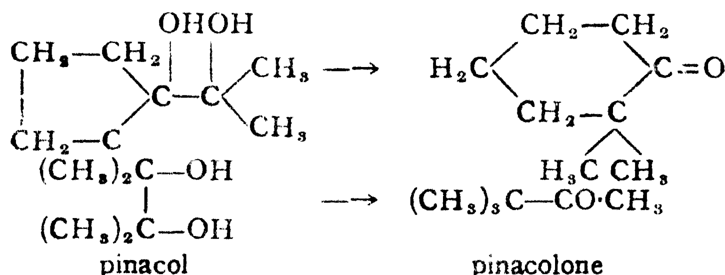
METHODS INVOLVING CHANGE IN THE SIZE OF THE RING :—A number of reactions are known which produce a change in the size of the ring. The exact nature of the driving force of these reactions is still undecided. It cannot be correlated in any simple manner with the condition of strain present in the ring. Sterical factors so far not discovered, may play an important part in such reactions. The methods can be classified as *(a)* ring expansion methods and *(b)* ring degradation methods.

(1) THE DEMJANOW REARRANGEMENT :—This is a general method for ring expansion. It consists in the action of nitrous acid on the cyclo-alkylamines.

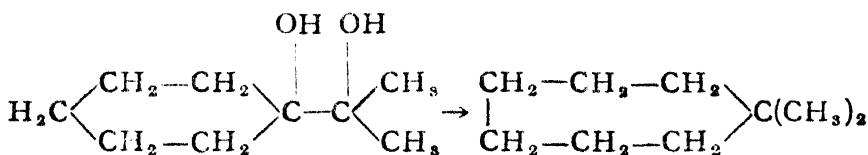


In the similar way, rings containing five, six and eight carbon atoms have been transformed into higher ring systems.

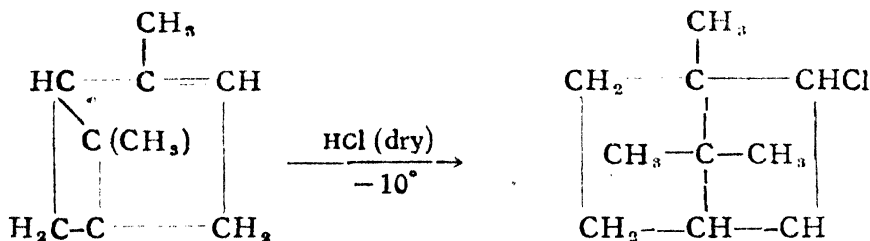
(2) THE PINACOL–PINACOLONE REARRANGEMENT :—Meerwein has investigated the re-arrangement reaction given by cyclic pinacols.



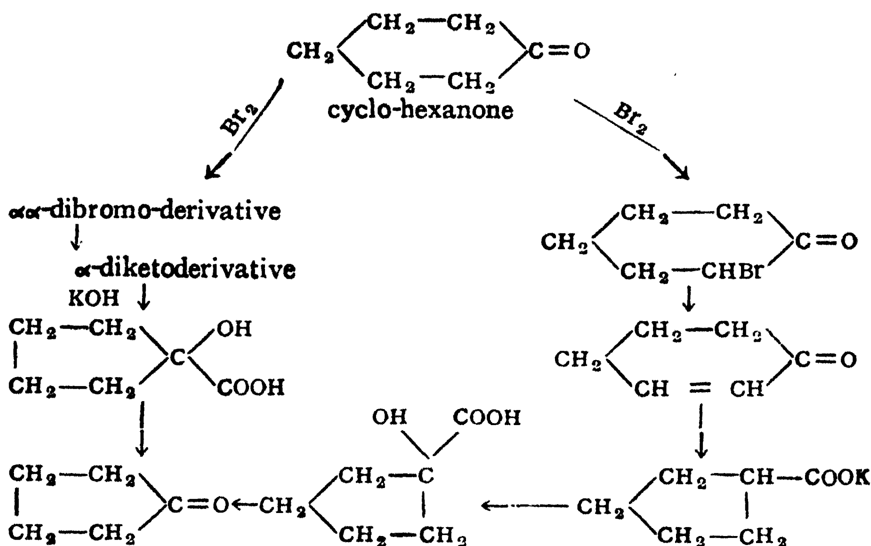
Even a cyclo-hexane ring may be expanded to a cycloheptane ring.



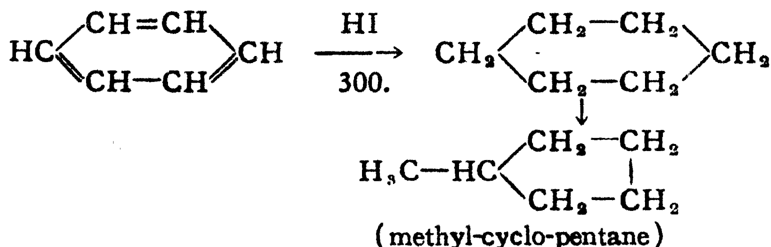
Addition of hydrochloric acid to α-pinene gives bornyl chloride. This involves a change from a four to a five-membered ring.



Wallach has reported methods by which degradation of a higher to a lower ring system may be effected. Thus, cyclohexanone can be transformed into cylopentanone. The method involves the action of alkali on the bromo-derivative of the higher system :—



There are other examples of ring contraction; benzene on reduction with hydriodic acid at 300°C is partially converted into methyl-cyclo pentane.



(methyl-cyclo-pentane)

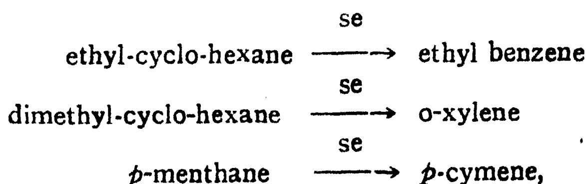
Recently, Nenitzescu has reported the reversible formation of methyl-cyclo-pentane from cyclo-hexane under the influence of aluminium chloride. This is the first case of dynamic isomerism between hydrocarbons.

It is interesting to observe that the ring expansion or contraction takes place only when the side-chain contains a reactive group like *OH* or NH_2. Further, in any ring change, it is always one carbon atom that is included (ring expansion) or displaced (ring contraction). For a long time, it was believed that these transformations had as the driving force, the diminution in ring tension of the system. Thus, the expansion of smaller rings and contraction of larger rings found a ready explanation. However, the recent work, wherein the

conversion involving a change from five to six-membered ring or *vice versa*, has been definitely established, throws much doubt on the original hypothesis of ring tension as the sole factor influencing such reactions. As is true, the small rings appear to be under great strain. At the same time large stable rings are known. It is thus evident that the tension in the molecule is not the only controlling factor. There are other influences which often determine the stability of the molecule.

GENERAL PROPERTIES OF THE ALICYCLIC COMPOUNDS :—The fundamental reactions of the alicyclic compounds can be grouped into two parts: (*i*) those of the *six-membered rings* and (*ii*) those of the compounds containing *three, four, five, seven* etc. carbon atoms.

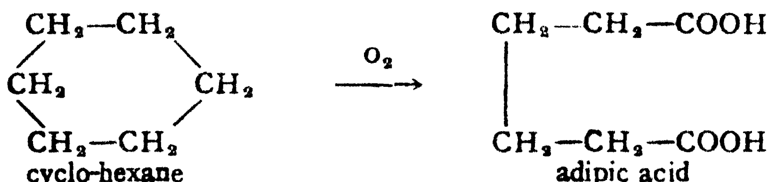
The primary reactions of *six-membered* ring systems are:— (*a*) Dehydrogenation to aromatic compounds:—This is effected by heating the alicyclic compounds with sulphur or selenium (Vesterberg). Better results have been obtained with the use of selenium, the hydrogen being eliminated as hydrogen selenide. The use of sulphur has the disadvantage that it may react further to form aromatic sulphur compounds. The less reactive selenium shows no such tendencies. Recently, Pd/C at 200–220 has been used as an efficient dehydrogenating agent. Cyclohexane is thus converted into benzene.



It is believed that the dehydrogenation proceeds *stepwise*, two hydrogen atoms being eliminated at each step. These dehydrogenation reactions have been of great value in the elucidation of the constitution of naturally occuring compounds like sterols, bile-acids, sex-hormones, alkaloids, and the sesquiterpenes. All these compounds contain the alicyclic systems which are readily converted into the easily identifiable aromatic compounds.

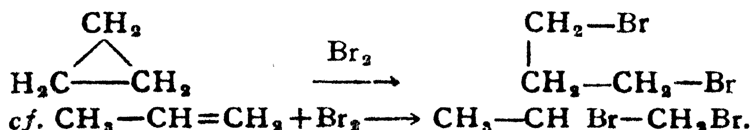
(*b*) Rupture of the C—C linkage to give open chain compounds. This is effected by vigorous oxidation; catalytic hydrogenation cannot cause cleavage readily. On vigorous oxidation with nitric

acid or with $KMnO_4$, the six-membered ring suffers fission and a dibasic acid of the succinic acid series is obtained. Cyclo-hexane is thus oxidised to adipic acid with nitric acid.

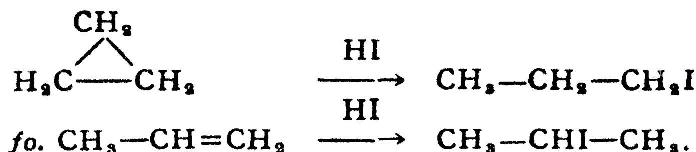


(The acid contains the same number of carbon atoms as the original hydrocarbon).

The typical reactions of the other ring systems are: The behaviour of cyclo-propane is different from that of other members. Cyclo-propane is thus readily opened up by heat and by other reagents like bromine or hydriodic acid.

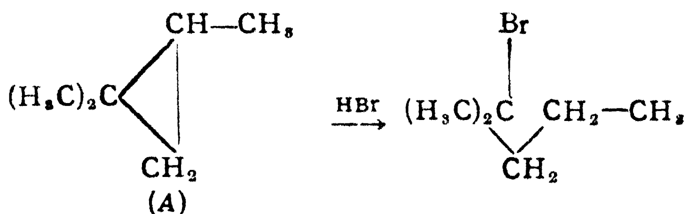


With hydriodic acid, we have :—

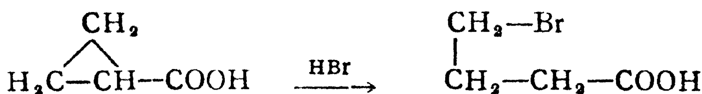


However towards potassium permanganate and ozone, cyclo-propane, in sharp contrast to propylene, exhibits great stability. The stability of the ring system is greatly affected by the nature and position of the substituents present in the ring. Alkyl groups are known to decrease the stability of the rings while the ring appears to be greatly stabilised by the presence of *COOH* groups. Further the stabilising effect is greatly marked when the carboxyl groups are situated on different carbon atoms.

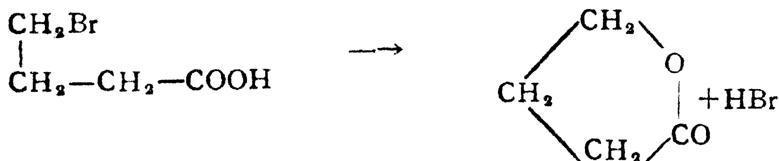
Conant and Kohler have investigated the influence of substituents on the ease of addition to the cyclo-propane systems. Their results indicate that the substituents have the same influence on the mode of addition to the cyclo-propane system, as to the olefin linkage. They have found that the addition of hydrobromic acid to cyclo-propane and its derivatives is influenced by the number and position of the alkyl groups. Thus, with (*A*), we observe:



(*i*) the ring opens up between the carbon atoms that hold the greatest and the smallest number of alkyl groups, (*ii*) halogen atom attaches itself to the carbon atom with the largest number of alkyl groups. With cyclo-propane, cyclo-propane acids or ketones, the opening of the ring is analogous and leads to the formation of γ-bromo-acids :—



The free acid may then suffer elimination of hydrobromic acid and give a lactone :--



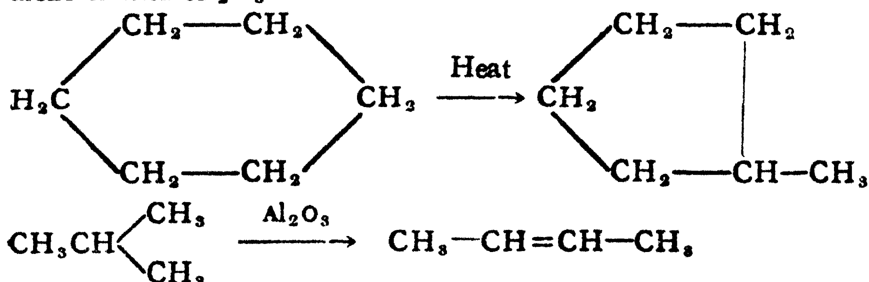
Again, hydrobromic acid readily attacks 1-1-dicarboxylic cyclo-propane giving bromo-ethyl malonic acid $BrCH_2—CH_2—CH(COOH)_2$; the isomeric 1-2-dicarboxylic acid is not affected even when heated with the reagent.

From the foregoing, it is obvious that the mode of addition to a cyclo-propane system is in close agreement with the Markownikoff's rule. There is, therefore, no fundamental difference between cyclo-propane and olefinic compounds. (Baeyer suggested that ethylene be regarded as the first member of the cyclo-paraffins).

Cyclo-butane and the higher homologues show no reactivity at all towards hydrobromic acid. Bromine, while it readily opens the cyclo-propane ring gives with cyclo-butane and higher homologues, substitution products. This corresponds to the behaviour of aliphatic compounds. In all chemical properties which do not involve the opening up of the ring, the cyclo-paraffins and their derivatives show great resemblance to the corresponding aliphatic compounds. The

various functional groupings when attached to the ring system manifest with slight modifications the usual characteristic reactions. The ring of cyclobutane and of other homologues is opened up by : (a) high temperature, (b) HNO_3 and (c) with H_2 in presence of Ni-Hydrogenation opens up all the rings except the six-membered one ; the temperature at which, the ring opens up is a measure of the stability of ring.

The alicyclic campounds also undergo isomerisation on heating alone or with Al_2O_3.



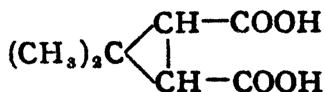
Also they show a few reactions which involve the expansion or contraction of the ring.

SOME IMPORTANT MEMBERS OF THE CYCLO-PARAFFINS

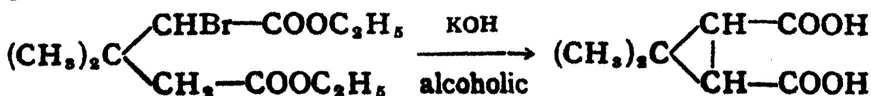
Herein will be discussed a few individual cyclo-paraffins including some carboxylic derivatives which are the products of oxidation of some of the natural terpenes and camphors, and the important natural products like muscone, civetone and chaulmoogric acid.

CYCLO-PROPANE GROUP : Cyclo-propane is a gas used as a general anæsthetic. It is obtained by the action of Zn on an alcoholic solution of 1, 3 dichloropropane in presence of NaI.

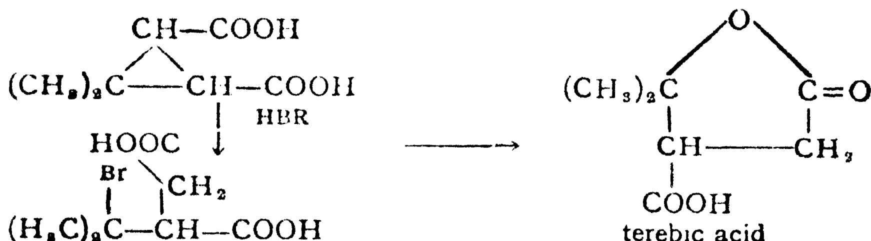
CARONIC ACID :—It is a cyclo-propane derivative. It is obtained by the oxidation of carone with hot acid potassium permanganate. It has the structure :—



i.e., 1-1-dimethyl (gem-dimethyl) 2-3-dicarboxylic cyclo-propane. It has been sythesised by Perkin and thorpe, from α:bromo-dimethyl glutaric ester by the action of alcoholic potash :—

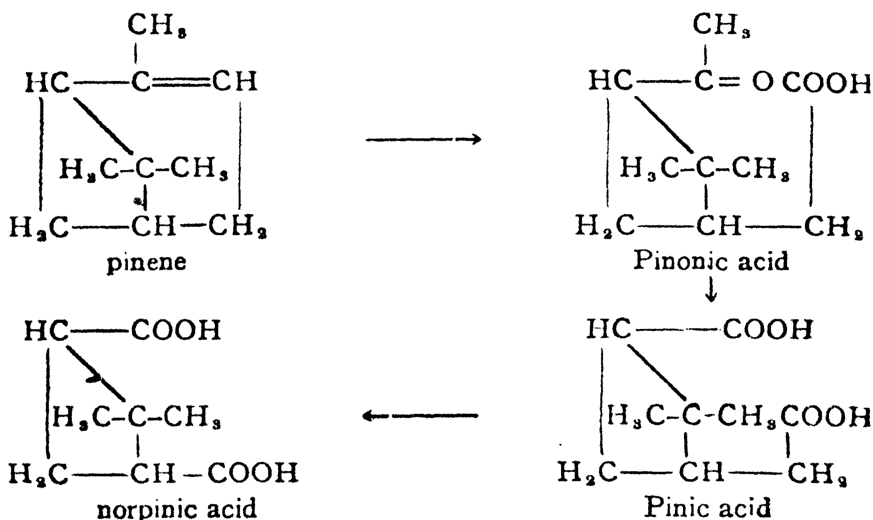


It is known in *cis* and *trans* forms. The *trans* modification has been further resolved into its optical enantiomorphic forms of specific rotation of ± 38·5. On heating with hydrobromic acid at 100°, it is converted into the isomeric terebic acid :—



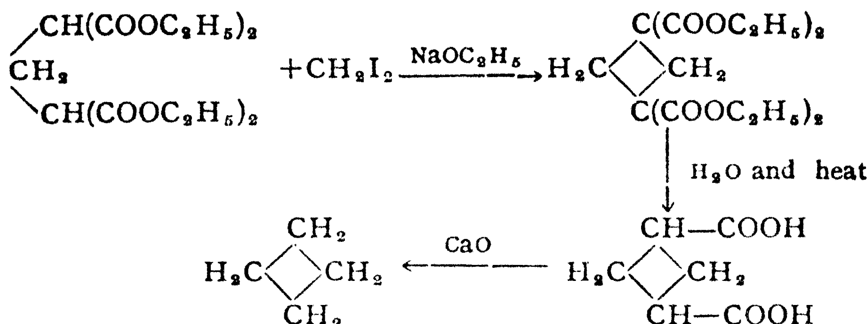
Terebic acid is obtained by the graded oxidation of ∝ terpineol molecule with alkaline and acid potassium permanganate.

CYCLO-BUTANE GROUP: PINONIC, PINIC AND NORPINIC ACIDS: Pinene on oxidation gives successively pinonic, pinic and norpinic acids which are all cyclo-butane derivatives :—



Norpinic acid has now been synthesised by Kerr. The synthesis of cyclo-butane systems offers a unique problem. The usual methods of forging three, or five-membered rings fail when applied to cyclobutane. Some of the important methods devised for the synthesis of this system are :—

(*a*) Perkin's method :—



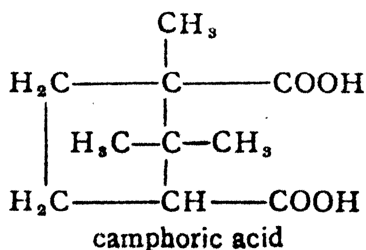
(See also the synthesis of norpinic acid by Kerr).

(*b*) Another method consists in the polymerisation of unsaturated compounds. Thus, we have in general :—



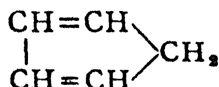
The process is accelerated by heat, light and by the action of acids or alkalies. Truxillic and iso-truxillic acids are obtained by an analogous condensation of cinnamic acid (see p. 178). They are found in the cocoa leaf and in the alkaloids of cocaine. They are readily coverted into cinnamic acid by distillation. On oxidation, benzil is formed, thus indicating the presence of the grouping, $C_6H_5—C—C—C_6H_5$ in the r molecules. They are of great stereochemical interests. Thoretically, five stereo-isomers are possible : all of them are known and their configurations assigned by Stoermer.

Cyclo-pentane Group :—One of the most important and longest known compounds belonging to this group is *camphoric acid.* It is the product of oxidation of camphor with nitric acid and has been assigned the formula :—

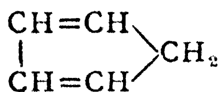


camphoric acid

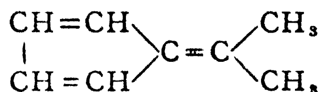
Its synthesis has been achieved by Komppa, Perkin and others. Another interesting compound of this system is *cyclo-pentadiene.*



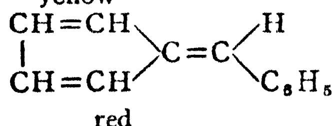
It contains the conjugated system of double bonds and hence, it is very reactive. The CH_2 group is characterised by great reactivity comparable to that of the CH_2 group of the malonic acid system. It readily undergoes condensation with aldehydes and ketones to give coloured hydrocarbons called '*fulvenes*' The condensation occurs in alkaline solutions *i. e.* sodium ethoxide or alcoholic potash. The *fulvenes* constitute a class of coloured hydro-carbons. Some coloured *fulvenes* are :—

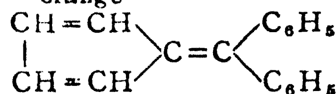


yellow



orange

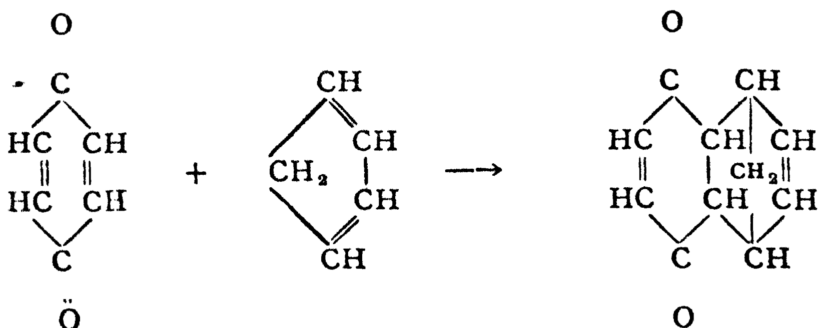




red

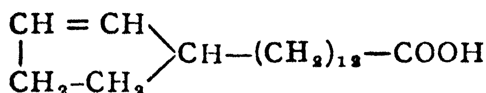
The cause of coloured in these compounds is the presence of conjugated systems. The deepening of colour follows the gradual loading of the molecule.

Cyclo-pentadiene adds on, by 1-4 addition, to unsaturated molecules (Diels and Alder's reaction). Thus, *p*-quinone and cyclo-pentadiene react to form a condensed endocyclic system.

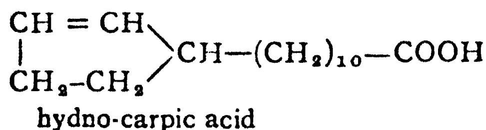


CHAULMOOGRIC ACID :—It is a constituent of the oil chaulmoogra. The oil is obtained from the seeds of the fruit of *Taraktogenus*

kursii—a tropical tree. The oil is used in the treatment of leprosy. The acid is a cyclo-pentene derivative and has the structure :—



The above structure has been confirmed by a synthesis of *dl*-chaulmoogric acid by Perkin and Cruz. Another related acid found in the chaulmoogric oil is hydno-carpic acid :—



hydno-carpic acid

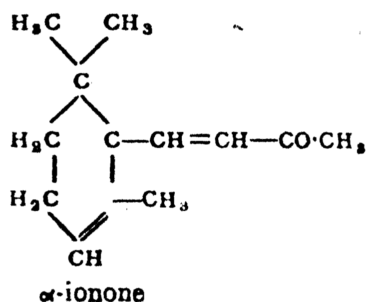
At present, the ethyl esters of the Na salts are used in the treatment of leprosy. The natural oil which is a glyceride, produces nausea and gastric irritation.

CYCLO-HEXANE GROUP :—The cyclo-hexane system occurs in the naphthenes of the petroleum and in the terpenes and camphors which constitute the natural "*essential oils*". A large number of them have been synthesised, first by reactions which take place *intra-molecularly* in the 1-6 position and secondly, by hydrogenation of aromatic compounds. The reduction is carried out by nascent hydrogen from a metal combination like sodium and alcohol or by the catalytic hydrogenation with molecular hydrogen in the presence of finely divided metals such as *Ni*, *Pt* and *Pd*.

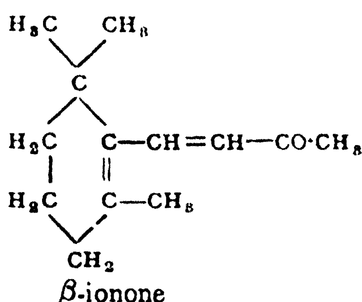
Cyclo-hexane :—C_6H_{12} is obtained from C_6H_6 by hydrogenation with nickel as a catalyst. It is liquid b. p. 81°. In its chemical behaviour, it closely resembles the paraffins. Oxidation with hot acid potassium permanganate gives adipic acid. The adipic acid can be converted into the amide or into hexamethylene diamine, both of which are used in the manufacture of the synthetic fibre ***nylon***.

In the above reaction, there, is a method of converting the aromatic cyclic system into an open-chain system. This is the reversal of the Wislicenus' method of building up a cyclic system from the open-chain dibasic acids. Cyclo-hexane and its derivatives can also be readily dehydrogenated into aromatic compounds, by the action of selenium or sulphur.

Two cyclo-hexane derivatives of commercial importance are the α-and β-ionones. They form the well-known 'synthetic violet perfume.



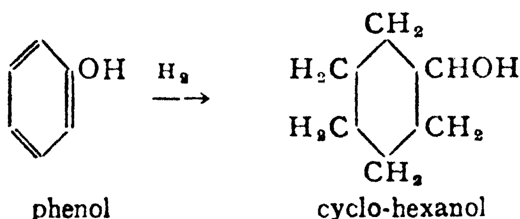
α-ionone



β-ionone

They are obtained from pseudo-inone (q.v.) by the action of barium hydroxide.

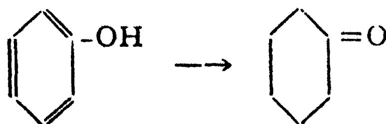
CYCLO-HEXANOL—This is rapidly becoming an important article of commerce. It is obtained from phenol by catalytic hydrogenation with H_2 and Ni at 180°. It has a camphorlike smell and hence is rapidly finding use in celluloid, soap and lacquer industries. It can be used as a motor fuel also. It is a liquid b. p. 160·5°C.



phenol cyclo-hexanol

On oxidation with chromic acid, it is readily oxidised to *cyclo-hexanone;* with nitric, acid, or by vapour phase oxidation cyclohexanol is converted into adipic acid.

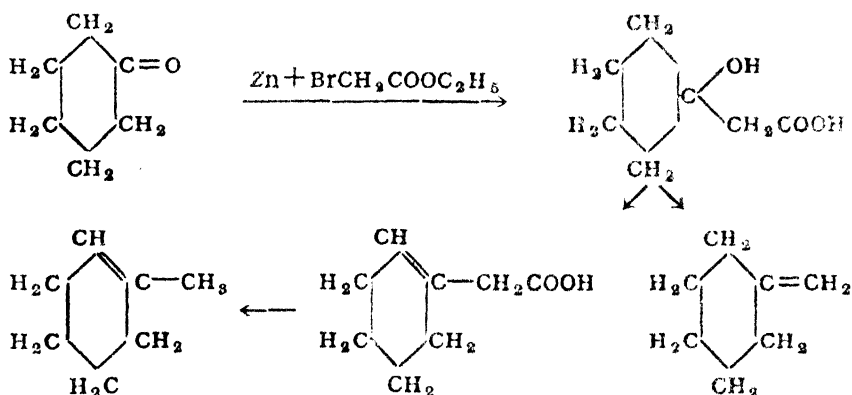
CYCLO-HEXANONE :—It is also obtained by the electrolytic reduction of phenol the latter is reduced to cyclohexanol which ketonises to cyclohexanone.



It forms an important synthetic material for the preparation of a large number and variety of hydrocarbons. It is very reactive, as

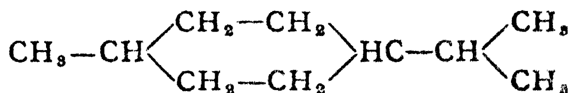
it contains the grouping CH_2—CO—CH_2—; the usual carbonyl reagents, hydroxylamine, phenyl-hydrazine give the usual corresponding condensation products. Benzaldehyde readily condenses to give the benzylidene derivative. On oxidation with acid $KMnO_4$ adipic acid is formed.

Wallach has extended Reformatsky's reaction to this ketone. Thus, we have :—



In this way, hydrocarbons related to the natural terpenes have been obtained by Wallach.

Para–MENTHANE :—It is prepared by hydrogenating *p*-cymene. It is a liquid (b.p. 170°). It is the parent substance from which the most important terpenes and camphors are derived.



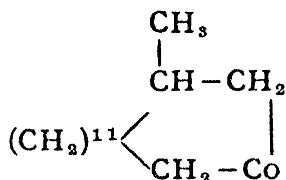
(Baeyer has called it '*terpane*' because of its relationship to the terpenes).

Cyclo–octa–tetra–ene is an unsaturated compound related cyclo-octane. It is an analogue of benzene. It was first obtained from pseudo–pelletierine, an alkaloid from pomegranate. It has been recently synthesised by Reppe by the polymerisation of acetylene under pressure, in tetrahydrofuran in presence of Ni $(CN)_2$ It is a golden yellow liquid (6.p. 142–143). Unlike benzene, it is highly reactive and shows the typical properties of an olefin. This is partly due to its nonplanar structure. It has the chair form and is not

stabilised by resonance as benzene is; the double bonds are all conjugated.

NATURAL COMPOUNDS WITH LARGE RINGS :—As late as 1926, a compound containing a single ring built up of more than six carbon atoms had not been discovered to occur in nature. It was Ruzicka's researches on muscone from the musk deer and civetone from civet cat that established the existence of such ring systems in these natural products.

Muscone isolated by H. Walbaum has the molecular composition $C_{16}H_{30}O$. It is a ketone and contains no double bond; hence it must contain a ring. The nature of the ring is revealed by reduction. On reduction with amalgamated zinc and hydrochloric acid it gives methyl-cyclo-penta-decane. The position of the CH_3 group is established by the results of ozonolysis of the benzylidene derivative of muscone. The benzylidene derivative gives on ozonolysis 2-methyl-tetra-decane-1, 14,*di*-carboxylic acid: (HOOC·CH·CH $CH_2)_{12}$ COOH· Muscone has been assigned the structure :—

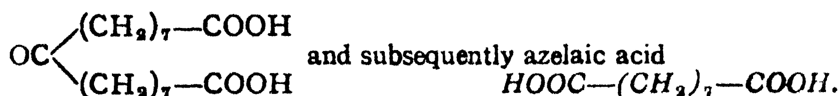


3-methyl-cyclo-penta-decanone-1.

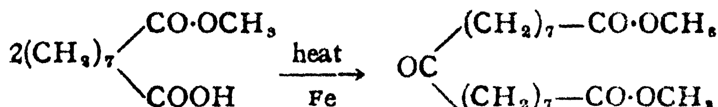
It is optically active. It is now replaced by the synthetic "*exaltone*" which is cyclo pentadecanone.

CIVETONE :—It was isolated by Sack from the civet cat. It is a glandular exudate. Its molar composition is $C_{17}H_{30}O$. Civetone gives a semi-carbazone which with $NaOC_2H_5$ gives a hydrocarbon $C_{17}H_{32}$ with one double bond. On oxidation, the latter is converted into a dibasic acid $C_{17}H_{32}O_4$; the same acid is obtained from dihydro with-civetone and is identical with $(CH_2)_{15}$ $(COOH)_2$. These results indicate that civetone may be a *monocyclic* unsaturated ketonic compound. Civetone on reduction, gives a dihydro-derivative which is identical with cyclo-heptadecanone. This indicates that civetone must contain a 17-membered ring and also a double bond. The position of the latter is revealed by oxidation studies.

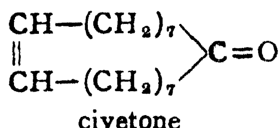
Oxidation of civetone with potassium permanganate gives a keto-dicarboxylic acid :



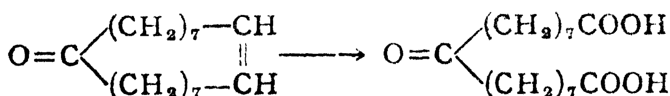
The keto-dicarboxylic acid was synthesised from the monomethyl ester of azelaic acid, which also establishes the position of the double bond :—



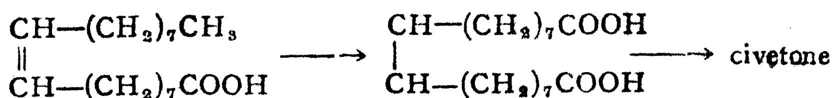
Hence, the structure for civetone is best formulated as :—



Such a formula would readily give the keto-dibasic acid on oxidation :—



The formation of civetone in nature probably takes place as follows : oleic acid undergoes ω-oxidation and the dibasic acid so formed loses CO_2 and gives civetone.

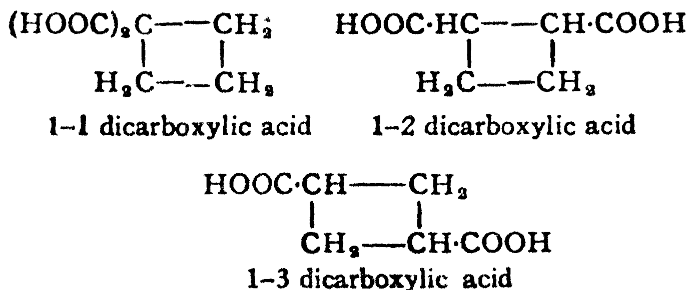


Isomerism Among the Alicyclic Compounds

We shall now discuss the different types of isomerisms manifested by the alicyclic compounds. Both structural and stereoisomerism are exhibited by the derivatives of alicyclic compounds, and they are more complex than those in the case of the corresponding isomeric olefins.

Structural isomerism :—The mono-alkyl derivatives of polymethylenes may show a kind of ring isomerism ; thus methyl

cyclo-propane is isomeric with cyclo-butane, and methyl cyclopentane is isomeric with cyclo-hexane. However in the case of other mono-substituted derivatives, no cases of isomerism are met with. In the case of di-and other poly-substituted derivatives, isomerism due to position of the substituent in the molecule is possible. Thus, in the case of tetra-methylene di-carboxylic acids the following isomers are possible :—



This type of isomerism is comparable to the position isomerism of the di-substituted benzene derivatives (*o*, *p* and *m* isomers).

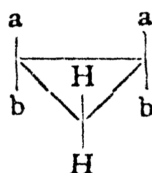
STEREOISOMERISM :—Stereoisomerism of both kinds, geometric and optical is manifested by these cyclic compounds. The geometrical isomerism exhibited by maleic and fumaric acids is conditioned by the presence of a double bond in the molecule which completely inhibits in free rotation of the carbon atoms thus joined. In the case of the alicyclic systems, free rotation about the single linkages is prevented by ring formation and gives rise to similar geometrical isomerism. At the same time, optical isomerism in consequence of the existence of a special type of molecular dissymmetry also becomes possible. Further the stereochemistry of alicyclic compounds involves considerations of the conditions and factors that defermine the relative stabilities and the relative ease of formation of the different rings of the alicyclic compounds.

GEOMETRIC ISOMERISM :—Since ring formation completely inhibits free rotation about a single linkage, a di-substituted derivative of a cyclo paraffin with two substituents on different carbon atoms would exist in two geometrically isomeric forms. The two forms would be represented by the cases : (*a*) when both the substituents are on the same side and (*b*) when they are on opposite side of the ring. Thus if we represent the rings by polygons lying in

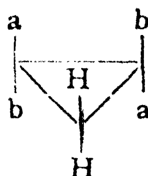
one plane (and there is sufficient experimental evidence for the coplanar configuration) at right-angles to the plane of the paper, and the two remaining valencies of each carbon atom by lines in the plane of the paper, one extending above and the other below the plane of the polygon, the configurations of the cyclo-paraffins will then be :—



A polymethylene with two or more different substituents would exist in *cis* and *trans* forms.

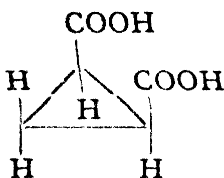


cis form

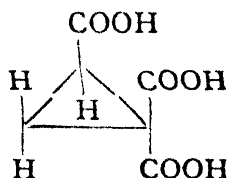


trans form

Thus 1–2 dicarboxylic-cyclo-propane would exist in two forms represented by *A* and *B*.



cis form *A*



trans form *B*

The number of such geometric isomers predicted by theory in all such cases, has been found to be in perfect agreement with experimental researches. However, these theoretical considerations especially the co-planar hypothesis for the polymethylene rings, hold good for small ring systems only. With larger rings containing six or more carbon atoms a *multi*-planar configuration has been definitely indicated and established by modern researches. (This will be dealt with in detail fully later on).

METHODS FOR THE IDENTIFICATION OF *Cis* AND *Trans* FORMS: A number of methods for the determination of the isomers have been developed. The most important and typical ones are those based on the following principles:

(*a*) Additional ring formation by the substituents: anhydride formation in the case of dicarboxylic acid derivatives.

(*b*) The detection of the presence or absence of molecular dissymmetry: the resolvability of a molecule.

(*c*) The formation and detection of a number of isomers by introduction of a new substituent or by elimination of the one already present in the molecule.

(*d*) Steric hindrance effects; in addition, there are a few empirical rules which are found to be useful as guides in indicating the actual configuration. These are:—(*i*) the Auwers-Skita rule and (*ii*) Skita's generalisation regarding catalytic hydrogenation.

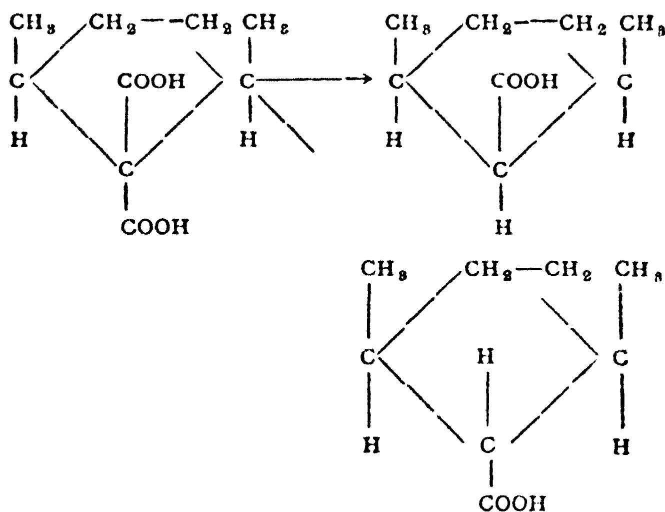
(*a*) ANHYDRIDE FORMATION:—This method is due to Baeyer. He found that of the two isomeric hexa-hydro-terephthalic acids, the one melting at 129°C readily lost water and gave an *anhydride* and the other which melted at 215° distilled off without decomposition He further concluded that the former was the *cis* isomer wherein the two COOH groups were favourably placed to form an anhydride. Thus, the fact that the COOH groups in *cis* position would more readily react with each other than those in the *trans* position, has been made the basis of a general method of determining the configuration of carboxylic derivatives. Camphoric acid, the product of oxidation of camphor with concentrated nitric acid, gives and anhydride and therefore, it must be represented by the *cis* form. The iso-camphoric acid must correspond to the *trans* form. But this method suffers from some practical limitations. The *trans* dibasic acids very frequently form anhydrides (Baeyer); and hence the mere fact that a dibasic acid gives an anhydride is not a proof that it is a *cis* acid. However, the *trans* acid anhydrides are less stable and rearrange into the *cis* anhydrides (Baeyer) *e. g.* the anhydride of hexahydro-phthalic acid. Therefore, of the two stereo-isomeric forms, in the case of the dicarboxylic acid derivatives of alicyclic compounds

the *cis* form is the one which is formed by the hydrolysis of the stable anhydride. The method, however, is limited to those dibasic acids which give the anhydrides. Further, it is not trustworthy for the acids containing large rings.

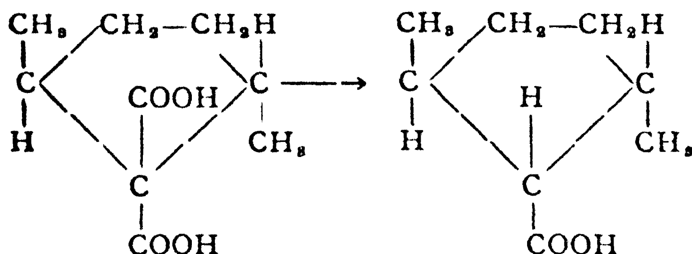
(*b*) CONFIGURATION FROM THE DETECTION OF THE PRESENCE OR ABSENCE OF MOLECULAR DISSYMMETRY :—This is one of the useful methods widely applicable. Werner and Conrad employed the method for the first time to confirm the configurations of the *cis* and *trans* modifications of hexahydro-phthalic acids. It is based on the stereo-chemical relationship of the two isomers; as a rule many *cis* modifications in consequence of the presence of two asymmetric carbon atoms of opposite sign are internally compensated and represented the *meso* modifications. The corresponding *trans* forms on the other hand, have an axis of symmetry and hence represent the racemic modifications which are 'resolvable' Thus of the two stereo-isomeric forms, the one that is resolvable into its optical enantiomorphs, is the *trans* modification while the non-resolvable corresponds to the *cis* form. This method is therefore readily applicable to compounds which contain carboxyl or other salt forming group.

(c) THE WISLICENUS' METHOD :—This method is based on the same general principle as Korners's "absolute method of orientation." As has been already indicated, of the two stereoisomeric forms, the *cis* has a plane of symmetry while the *trans* modification possesses only an axis of symmetry. Under these conditions, if a new substituents is introduced into the molecule at an atom placed symmetrically to those carrying the original substituents, the *cis* isomer would give *two* derivatives, while only *one* would result from the *trans* isomer. J. Wislicenus has developed a method which establishes the relative configurations of the isomers by a process which involves the elimination of a substituent present in the molecule. The cofiguration of the isomer is then deduced by the number of isomers obtained in each case. Thus the two forms of 2, 5-dimethyl cyclo-pentane 1, 1-dicarboxylic acids are distinguished by the number isomers formed by the loss of carbon dioxide from the *cis* form leads to two monobasic acids, while the *trans* gives only one :—

(*a*) *cis* forms:



(*b*) *trans* form:



The dicarboxylic acid with the m.p. 192°–104° on decarboxylation gives a mixture of two *mono*-basic acids. Hence it is the *cis* modification.

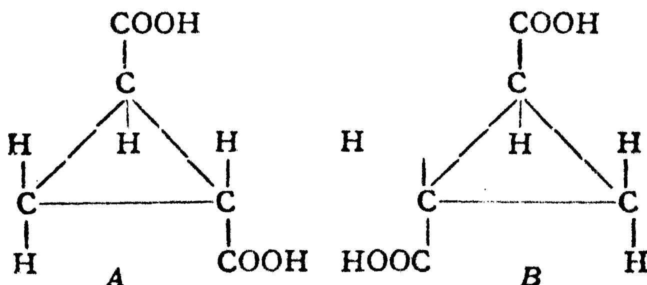
(*d*) Steric Hindrance Effects:—Steric influences which cause considerable differences in the reactivity of the stereo-isomers, have been made the basis of a practical method of determining the configuration by Vavon. Thus, of the two forms of 2-isopropyl cyclohexanol, one is esterified much more rapidly than the other. It is obvious that the less reactive isomer corresponds to the *cis* modification, the slower reactivity being ascribed to the steric effects exerted by the alkyl group in the *cis* position on the attack of the reagent on the hydroxyl group.

(*e*) Physical Properties:—An identification of the two forms can be effected by a study of the physical properties. Generally, the *cis* forms possesses a lower melting-point and greater

solubility. On heating with hydrochloric acid, the *cis* form is converted into the *trans* form.

The Raman spectra have proved of some value in the study of *cis* and *trans* isomerism. In the case of these isomers, the *cis* form has always a lower value by 16-20 units than *trans* ; the presence of even a small quantity of the *cis* in the *trans* isomer can be readily detected.

OPTICAL ISOMERISM :—Many of the polymethylene derivatives *e.g.* 1–2 dicarboxylic cyclo-propane, menthol, terpinol etc. exhibit optical isomerism. This is the result of molecular asymmetry caused by the presence in the molecule of one or more asymmetric carbon atoms. Thus, menthol has three asymmetric carbon atoms, and terpineol one. In the case of dicarboxylic derivatives like 1-2 dicarboxylic cyclopropane and hexahydro phthalic acid, the isomerism may be due to the geometrical conditions which are necessary for the non-superposability on the mirror-image. These conditions are the absence in the molceule of (*a*) a plane of symmetry, (*b*) a centre of symmetry and (*c*) an alternating axis of symmetry. Thus, *cis* hexa-hydro phthalic acid possesses a plane of symmetry and exists in one form only. The *trans* isomer which does possess the geometrical conditions necessary to confer non-superposability, exits in optically active enantiomorphous forms. These results have been experimentally verified by the researches of Werner and Conrad. Similarly, the *trans* form of 1–2 dicarboxylic cyclo-propane has neither a plane nor a centre of symmetry and hence exits in a racemic form. The corresponding *cis* form contains two asymmetric carbon atoms of opposite signs and therefore, the molecule represents a *meso* modification. The formula for the *trans* acid may be written as follows :—



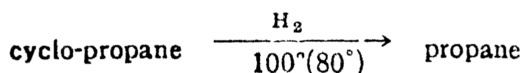
i.e., the two forms *A* and *B* cannot be superimposed on each other and

hence they exist in optically active form; one is the mirror-image of the other.

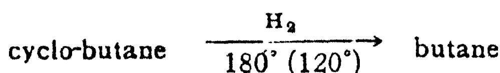
STEREO-CHEMISTRY OF ALICYCLIC COMPOUNDS

The stereo-chemistry of the ali cyclic compounds involves the study of the factors that influence (*a* the relative stabilities of the rings as indicated by the relative ease with which the rings are opened up and (*b*) the relative ease of formation of the rings from open chain compounds.

THE RELATIVE STABILITIES OF THE DIFFERENT RING SYSTEMS :—Willstatter and collaborators have carried out extensive researches on the relative stabilities of the rings. The relative degrees of stability of the different polymethylene rings are indicated by the relative ease with which they react with bromine or hydrogen to form open chain compounds, with the fission of the rings. Thus the temperature necessary to effect hydrogenation is a measure of the degree of stability of rings. Willstatter found that the temperatures of which the cleavage of the ring takes place in the case of the different phymethylenes are :



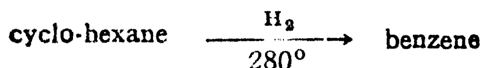
cyclo-propane $\xrightarrow[100^\circ(80^\circ)]{H_2}$ propane



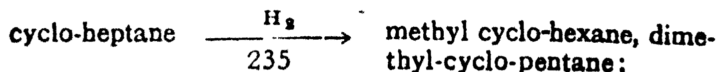
cyclo-butane $\xrightarrow[180^\circ\ (120^\circ)]{H_2}$ butane



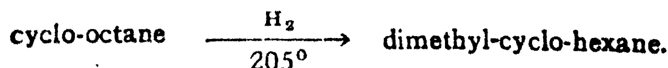
cyclo-pentane $\xrightarrow[300^\circ\text{-}315^\circ]{H_2}$ pentane



cyclo-hexane $\xrightarrow[280^\circ]{H_2}$ benzene



cyclo-heptane $\xrightarrow[235]{H_2}$ methyl cyclo-hexane, dimethyl-cyclo-pentane;



cyclo-octane $\xrightarrow[205^\circ]{H_2}$ dimethyl-cyclo-hexane.

The cyclo-propane and cyclo-butane systems therefore readily form open chain compounds, whereas cyclo-pentane requires a high temperture and the cyclo-hexane ring is not ruptured; on the other

hand cyclo-heptane and cyclo-octane rings are transformed into cyclo-pentane or cyclo-hexane systems. Thus, among the cyclo paraffins and their derivatives, the five and six-membered rings are the most stable, the stability of rings contaning more or less carbon atoms, being less and less. The greater stability of the five-and six-membered ring is also emphasised by the fact that many natural animal and vegetable compunds contain usually a five- or six-membered carbon framework.

STRAIN THEORY

The foundation of the stereo-chemistry of these cyclic compounds was laid by Baeyer who advanced his Strain Theory which constitutes an ingenious and very plausible explanation of these observed phenomena, Baeyer postulated that:

(*i*) the four valencies of the carbon atom are directed towards four corners of a regular tetrahedron, when they make with one another and angle of $109^\circ{\cdot}28'$; this is called the tetrahedral angle.

(*ii*) the directions of these valencies may be altered, but any such alteration, will produce a strain which shall be proportional to the amount of the deviation or distortion.

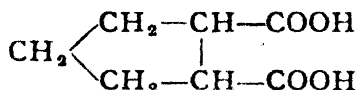
(*iii*) all the carbon atoms constituting the ring of the polymethylene lie in one and the same plane, so that a certain amount of deviation of these valencies from their normal positions, occurs in the formation of the ring.

Hence the degree of stability of such a ring or cyclic system would be *inversely proportional* to the amount of deviation. The angle of deviation for the cyclo-paraffins with different ring systems would then be:

$$\text{cyclo-propane, } \mu = \tfrac{1}{2}(109^\circ{\cdot}28' - 60) = 24^\circ{\cdot}44'$$
$$\text{cyclo butane, } \mu = \tfrac{1}{2}(109^\circ{\cdot}28' - 90) = 9^\circ{\cdot}44'$$
$$\text{cyclo-pentane, } \mu = \tfrac{1}{2}(109^\circ{\cdot}28' - 108) = 0^\circ{\cdot}44'$$
$$\text{cyclo-hexane, } \mu = \tfrac{1}{2}(109^\circ{\cdot}28' - 120) = 5^\circ{\cdot}16'$$
$$\text{cyclo-heptane, } \mu = \tfrac{1}{2}(109^\circ{\cdot}28' - 128{\cdot}34) = -\ 9^\circ{\cdot}33'$$
$$\text{cyclo-octane, } \mu = \tfrac{1}{2}(109^\circ{\cdot}28' - 135) = -\ 12^\circ{\cdot}45.$$

From these data, it follows that *five* and *six* membered rings should be the most stable, as in these systems the conditions of least

strain occur. A striking confirmation was almost immediately obtained by Perkin. He prepared a dicarboxylic acid containing a cyclo-pentane ring system :—



This compound was found to be very stable and thus ably vindicated the truth of Baeyer's theory. These conclusions are also borne out by the wide and common occurrence of such ring systems in many of the natural products. The naphthene and naphthenic acids present in natural petroleum are derivatives of cyclo-pentane and cyclo-hexane; also the ease of formation of 5 or 6 membered ring from compounds containing reactive groups in 1, 5 and 1, 6 position (Dieckmann's synthesis etc.) support the strain theory. Besides, there are some reactions of great significance from the standpoint of this theory; they are the Demjanow Rearrangement and the Wallach Degradation which involve a change in the size of the ring. We have many examples of expansion of smaller rings and of contraction of larger rings. These facts constitute strong evidence for the soundness of the strain theory. They imply that such transformations have as their driving force a diminution of ring tension.

LIMITATIONS OF THE THEORY :—There are some obvious limitations to the theory: (*i*) In strict accordance with the theory, the cyclo-pentane ring should be the most stable, even more stable than the six membered ring. This is not in close agreement with experimental facts, *i.e.* both physical and chemical evidence; cyclo-pentane ring can be opened up at 300° but cyclo-hexane cannot be opened up at all. Also, the cyclo-propane ring is formed more readily than the cyclo-butane ring; this is opposite to that predicted by the theory. (*ii*) The theory demands a pronounced variation in the stability of the different ring systems. The physical measurement data *e.g.* heat absorbed in the formation of the cyclic rings as given by Stohmann and Kleber are:—

cyclo-propane	38·1 K. cal.
cyclo-butane	42·6 (39·9) K. cal.
cyclo-pentane	16·1 K. cal.
cyclo-hexane	14·3 K. cal.

According to these data, cyclo-hexane ring is the most stable, while according to Baeyer, cyclo-pentane is the most stable. Further the difference between thermal data of cyclo-hexane and cyclo-pentane is very small, while, Baeyer's theory demands appreciable difference between them.

(*iii*) The abnormal figures obtained for cyclo-butane are of great interest as it has been repeatedly observed that the methods of synthesis of six, five and even three membered ring system fail when applied to the preparation of cyclo-butane derivatives. This theory offers no explanation for this observed discrepancy.

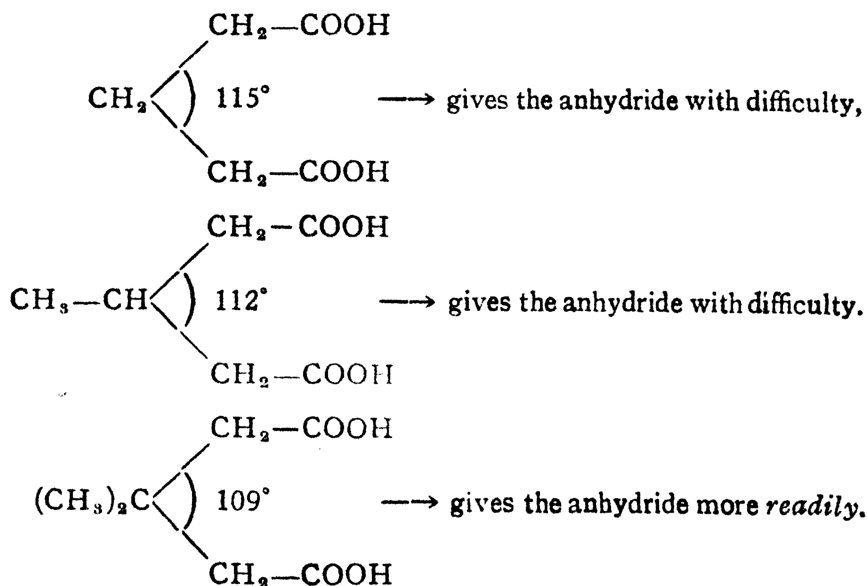
(*iv*) Recently transformation reactions are known which involve a change of a six to a five membered ring and *vice versa*.

(*v*) Examples of the stabilising effect on the ring caused by the presence of a substituent have also come to light. This indicates that there are factors other than ring tension that influence the stability of a ring; cyclo-propane is readily attacked by hydrobromic acid and by bromine with the fission of the ring. The mono-carboxylic acid derivative on the other hand, is stable to HBr below 170°. Bromine can only give a substitution product replacing the α-hydrogen atoms without opening the ring.

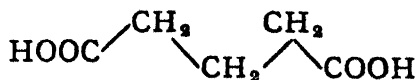
MODIFICATIONS OF THE STRAIN THEORY:—Two types of modifications have been introduced, based on the recognition of the fact that factors other than ring tension influence the stability of the rings. Firstly, it is now known that the tetrahedral angle is not fixed. It is alterable by the presence of substituents which affect the stability. This is the basis of the theory of valence deflection, postulated by Thorpe and Ingold. Secondly, it is now well-established that the carbon atoms constituting the ring, may not necessarily lie in one and the same plane and hence the stability depends on the form the ring assumes : the Sachse-Mohr hypothesis is based on this view-point.

THORPE-INGOLD'S MODIFICATION:—According to the Strain Theory, the tetrahedral angle—the angle between the carbon atoms constituting the ring—is the principal factor that determines the stability of the ring system. The theory also implied that ring formation was influenced by similar stereo-chemical factors chief among them being the inter-valency angle.

More recent work has however, shown that there are other factors than ring tension which control the stability and the formation of various ring systems. The effect of substituents in promoting ring formation had been long known. Auwers and V. Meyer have reported that methyl succinic and methyl glutaric acids yield the corresponding anhydrides more readily than the unsubstituted acids. They have further indicated that with the increasing number of substituents, the ease with which the anhydride is formed, also tends to increase. Recently extensive researches have been carried out by Thorpe and Ingold on the formation and stability of cyclic systems. They have conclusively established that the ring formation as well as stability of the ring is greatly affected by the following factors: *(i)* the angle between the carbon atoms constituting the closed ring and *(ii)* the nature of the substituents attached to the cyclic carbon atoms. Thus the effect of methyl and specially the gem dimethyl group $(CH_3)_2C$ in ready ring formation is illustrated in the case of formation of cyclic systems from methyl and dimethyl dibasic acids :—



The dibasic acids probably exist as :



and that the effect of methyl substitution is to cause an approximation of the carboxyl groups of the molecule which is necessary for their interaction, is established by the measurments of Ingold and Gane by the Bjerrum method. They give the following values for the distances between the *COOH* groups :—

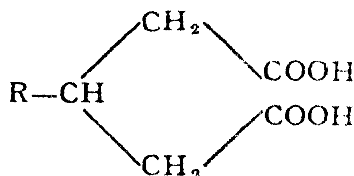
Glutaric acid, $\gamma = 9.22$ A°

β-methyl-glutaric acid, $\gamma = 2.27$ A°

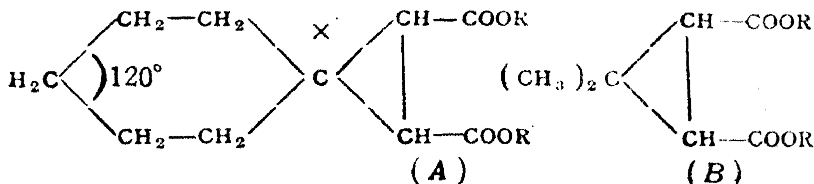
$\beta\ \beta$ *di*-methyl-gutaric acid, $\gamma = 1.57$ A°

The effect of methyl substitution is also to decrease the inter-valency angle (see above) which leads to ready ring formation.

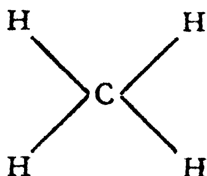
The acids then may assume the form which readily reacts to give the anhydride.



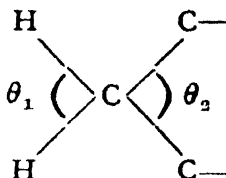
Similarly, influences which tend to decrease the angle between the carbon valencies, give easier ring formation and greater stability. Thus the spiro compound (*A*) containing a six-membered and a three-membered ring with one carbon atom common, is more easily made and is more stable than the cyclopropane derivative (*B*) containing only a three-membered ring. The explanation is that the increased angle of 120° in the sixmembered ring (A) tends to decrease the angle of the carbon atom marked with × and thus stabilises the three-membered ring system.



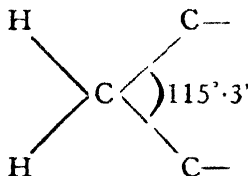
The above considerations have led Thorpe and Ingold to advance their theory of valence deflection. According to this theory, the tetrahedral angle 109°28' is to be formed only when the carbon atom is linked to groups of equal size as in methane :



But in the case of compounds containing :



θ_1 will be less and θ_2 greater than the normal tetrahedral angle ; this is due to the volume of the carbon atoms being larger than that of the H atoms. It is however, recognised that the hypothesis is essentially of a qualitative nature but is supported by sufficient experimental evidence. They have calculated the valence angles of the adjoining pair of carbon atoms in the following system, which is present in all polymethylene rings, based on the Traube's constants for atomic volumes of CH_3 and H and found it to be 115°-3'.



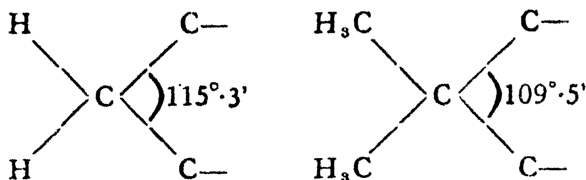
On the basis of this value, it is possible to calculate by how much the terminal C atoms of normal propane and butane chains, must approach one another to form cyclopropane and cyclobutane rings. The approach values are :

cyclo-propane O·345 ; cyclo-hexane O·207 ;

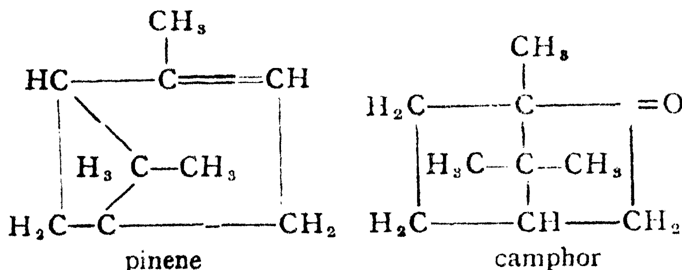
cyclo-butane O·427 ; cyclo-heptane O·730 ;

cyclo-pentane O·220 ;

These values are in good agreement with the thermal data (page 193). The effect of further substitution on the intervalency of the polymethylene system was shown to be as follows :—



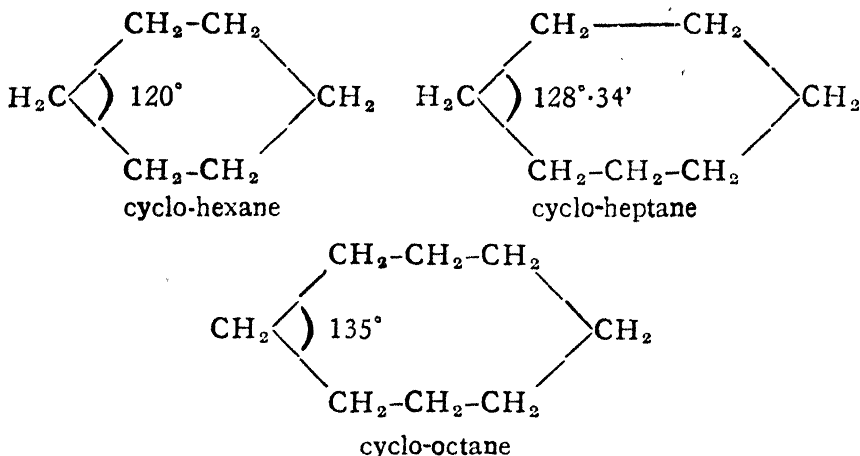
It follows therefore that the presence of methyl groups tends to depress the intervalency angle, *i.e.* the ring formation is facilitated. The attachment of two methyl groups (*gem* dimethyl) to carbon atoms involved in three, four and five-membered rings greatly augments the stability of the structure. Whilst if the ring contains seven or more carbon atoms, a decrease in stability would result. The effects of the gem-dimethyl group in relieving the strain inherent in small rings is further reflected in the structure of many natural products, *e.g.* pinene, camphor.



These molecules contain endo-cyclic systems with gem grouping: $(CH_3)_2C$ which confers great stability on these otherwise unstable systems.

Thus the Strain Theory of Baeyer with the necessary modifications, introduced by Thorpe and Ingold can give a rational and scientific account of the peculiar and complicated, stereo-chemistry of the alicyclic compounds. But it is limited to the cyclic systems with smaller rings (from three to eight carbon atoms).

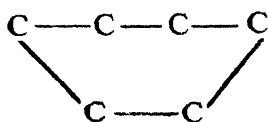
STRAINLESS RINGS :—We have seen that Baeyer in his Strain Theory assumed that carbon atoms of the alicyclic systems lie in one and the same plane. This involves the expansion of the valence angles in making a ring of more than six carbon atoms. For cyclo-hexane and other higher members, with more carbon atoms, the intervalency angle *i.e.* the tetrahedral angle will go on increasing :—



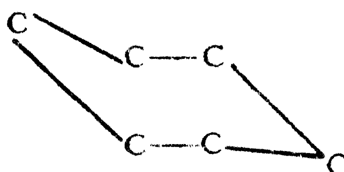
Thus the formation of large rings will involve negative strain. In fact, very large rings will involve an almost unbelievable strain and hence cannot exist according to this hypothesis. Before 1926, no compound containing a *single* ring of more than eight carbon atoms was known, but since then Ruzicka and his collaborators have prepared by the distillation of thorium salts, a series of cyclic ketones containing 17-32 carbon atoms in a *single* closed ring; and these higher members containing seven or more carbon atoms are found to be stable. Thus cyclo-heptadecane which according to the Baeyer's theory would have the valenecy deflection of—4°·41' is very stable towards fuming hydriodic acid and red phosphorus at 250° C. Its keto-derivative, cyclo-heptadecanone can be passed over thoria at 400°—420° without fission of the ring (Ruzicka and others).

Similarly, the natural products, muscone $C_{16}H_{30}O$ and civetone $C_{17}H_{30}O$ were also shown by Ruzicka to belong to this class of compounds and possess large single ring systems. Ruzicka's establishment of the constitution of these naturally occurring compounds constitutes one of the most triumphal achievement of modern times. The fallacy that large stable rings were incapable of existence was smashed and evidence for the existence of large rings was thus placed on an experimental footing. It then appeared that Baeyer's assumption that molecules of these compounds have co-planar structures was unwarranted. As early as 1890, Sachse had pointed out that in the case of cyclo-hexane and higher members, the angle whose polygon would be greater than 109°·5' *i. e.* the normal angle, the molecules

would take up multi-planar configurations whereby all the strain would be relieved and the normal valence angle retained. Thus the existence of large *stable* rings containing several carbon atoms could be readily accounted for This was the origin of the conception of "*Strainless rings.*" The assumption of the existence of strainless rings on a multi-planar configuration basis, leads to the corollary that these strainless molecules should exist in two or more stereo-isomeric forms. Thus in the case of cyclo-hexane—the sixmembered ring—the following two forms would be possible—



(A)



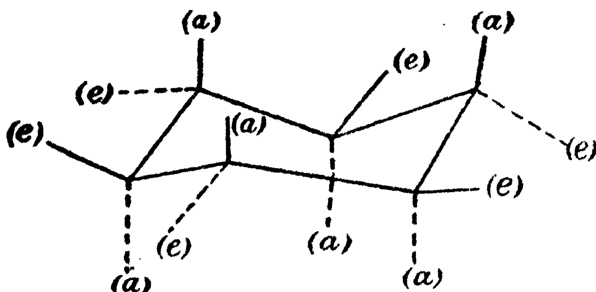
(B)

These forms are variously designated :—

'A' form = *cis* or C form or bod, boat or tub form.

'B' form = *trans* or Z form or chair form.

But so far there is no direct chemical evidence for the existence of the two different geometric forms of cyclo-hexane. Hassel has shown that the *chair* form of cyclohexane has a lower energy content at room temperature, than the *boat* form. Hence it is the preferred form; the term 'conformation' has been introduced to designate a particular form of spatial arrangement of a molecule when more than one such arrangement is possible. The orientation of bonds in the chair conformation of cyclo hexane in represented as :—



According to Hassel, there are two types of bonds : (1) equatorial (e) and (II) axial (a). The equatorial bonds radiate more or less in the plane of the ring. They are relatively very stable. The axial bonds are perpendicular to the ring and relatively unstable.

This concept of multiplanar or puckered rings has been very useful to account for many observed facts.

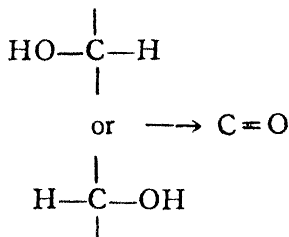
Wierl, by the method of electron ray interference has independently established the non-planar configuration of the cyclo-hexane molecule.

Baeyer had found that both the *cis* and *trans* hexahydrophthalic acids formed the anhydrides. If the *trans* acid possessed a ***planar*** configuration, the anhydride formation would involve considerable strain and hence would not take place at all. On the other hand, anhydride formation would be easy if the carbon atoms take up a multiplanar strainless configuration in which the two carboxyl groups would come near each other as in the *cis* form. Recently, Windaus, Huckel and others have reported that both the *cis* and *trans* forms of hexa-hydro-homo-phthalic acid readily give the anhydride. This is only possible if the *trans* acid takes up a strainless configuration when the two carboxyl groups are brought into a favourable position to form the anhydride.

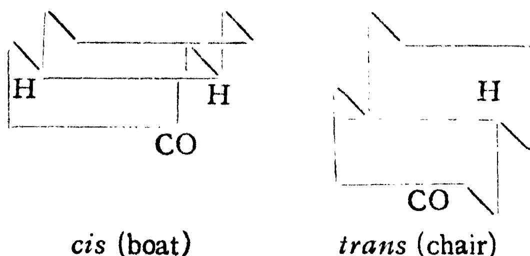
However, in the case of many such systems, the stereoisomeric forms have not been actually isolated. This difficulty has been overcome by Mohr who has suggested that these stereoisomeric forms in the case of simple higher cyclo-paraffins and their derivatives, are mutually interconvertible and really represent rapidly interchanging states, as the position of the carbon atoms in the ring fluctuates continually. The models of the two forms of the cyclohexane have been constructed and it has been found that they can be converted into each other by the application of gentle pressure. However, if two such strainless rings are condensed together as in decahydro-naphthalene where the possibility of fluctuation between two forms is excluded, the two relatively stable stereo-isomers must be capable of existence. Actually, the *cis* and *trans* forms of decahydronaphthalene have been isolated. Both are very stable towards heat. The *cis* form on long contact with $AlCl_3$, is quantitatively converted into the *trans* form (Zelinsky, Turowa-Pollak). As a rule the *trans* form of decalin and

its derivatives are more stable than the *cis* form. This is the Sachse-Mohr hypothesis for the strainless rings.

An independent confirmation of the existence of strainless *cis* and *trans* modifications of decalin and its derivatives has been obtained by Huckel and his collaborators. They obtained by reduction of β-naphthol, two stereo-isomeric β-decalols. On oxidation, the decalols give two different ketones, decalones. If the two decalols had represented the *cis* and *trans* isomers of the same decalol, the ketone formation would have eliminated the difference:—



The two decalols and the two decalones therefore should differ in configuration.



cis (boat) *trans* (chair)

These configurations have been further confirmed by oxidation of the decalones to the *cis* and *trans* forms of 2-carboxy-cyclohexyl propionic acid $HOOC.C_6H_{10}.CH_2.CH_2COOH$. Other examples, besides decalin, are now known, of dicyclic compounds consisting of a pair of condensed six membered rings which exist in the strainless *cis* and *trans* forms.

The existence of "strainless" structure is thus an experimental fact. It is obvious that except in the case of tri, tetra and penta-methylenes, the polygons of the carbon atoms of the higher members and their derivatives form multi-planar configurations. This will indicate a rapid increase of stability as we pass from tri-methylene to penta-methylene, the higher members being all more or less *equally*

stable. The observed chemical behaviour of the alicyclic compounds actually corroborates such a conclusion. This conclusion is also supported by the recent studies of Huckel on (i) the heat of combustion and (ii) the molecular volumes of the cyclo-paraffins. The values are tabulated below :—

Number of C atoms in the ring	*Heat of combustion per gram-mol*	*Heat of combustion for each CH_2 group*
2	340	170
3	505	168
4	662	165
5	797	159
6	950	158
7	1,103	158
8,15,17,30	—	157–157·5

The above results show clearly that the heat of combustion for each CH_2—, tends towards 157°·5; and this is the value for the heat of combustion for each CH_2, in the case of straight chain paraffins. The latter are built up of several CH_2 groups arranged in long chains which are very stable. Hence it follows that the polymethylenes which are also built up of many CH_2 groups, must exist in stable forms.

Molecular volume of CH_2 in these compounds has been determined; it decreases continuously from the 4–C system to the 10–C system (*viz.* 20·4→16.3) and then practically remains constant at 16·3. The latter value corresponds to the value of the CH_2 group in aliphatic compounds. Thus, these results indicate that there is a small strain in the smaller rings containing three and four carbon atoms, while the strain is absent in the cyclo–pentane and higher ring systems.

Lastly, the X-ray investigations of Muller also support this view. According to his results, rings with more than 20 carbon atoms consists of parallel double chains, the straight portions of which are identical with *n*-paraffins in structure.



(The atoms retain the tetrahedral angle)

Drew (1933) has pointed out that in the case of monocyclic compounds it is possible for the carbon atoms to form axially symmetrical, planar polygonal configurations which will be almost strainless.

CHAPTER IV

TERPENES AND CAMPHORS

INTRODUCTION :—Terpenoids or Terpenes and camphors are widely distributed in nature in the conifera and citrus kingdom *e. g.* the pines, the firs and the citrus trees. The oils obtained by distilling tissues, saps, and leaves of the above plants are mixtures of organic compounds, characterised by a distinct pleasant smell and hence are called essential or ethereal oils. The constituents of these essential oils are the various terpenes and camphors. One of the most important and typical essential oils is the oil of turpentine. It is obtained from the pine tree. Its chief consituent is pinene. It also contains other complex *resins* also called colophony. Oil of turpentine is commercially a very useful product. It is insoluble in water but is miscible with organic solvents. It dissolves iodine, sulphur, resins and rubber. Hence it finds extensive application in the preparation of varnishes and paints.

Other common essential oils with their chief constituents are :—

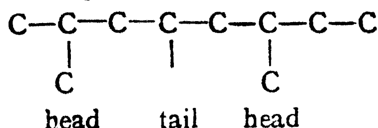
Oil of cardamom, Oil of Cajeput	⟶	Terpineol
Oil of Caraway	⟶	Limonene
Oil of lemon grass	⟶	Citral
Oil of camphor	⟶	Camphor
Oil of roses, geranium, lavender	⟶	Geraniol, Linalool
Oil of eucalyptus	⟶	Cineole
Oil of peppermint	⟶	Menthol, Menthone.

Many of these essential oils find application in medicine and perfumery. They act as powerful antiseptics.

GENERAL BEHAVIOUR AND COMPOSITION :—Most of the terpenes and camphors are colourless, pleasant smelling and highly refractive liquids; they are volatile in steam. Many of them are optically active while some are racemic. They are *unsaturated* and they readily give addition compounds with ozone, halogens, halogen acid, nitrosyl chloride and oxides of nitrogen;

many of these addition products are well-defined crystalline compounds which have served for their isolation and identification. Chemically, the essential oils are mixtures of unsaturated hydrocarbons, alcohols, aldehydes and ketones. Ethers are also known to occur as natural products ; the most important and widely distributed is cineole. The empirical composition of the terpenoids is given by the formulas $(C_5H_8)\,n$ of $(C_5H_8)\,nO$. The unsaturated hydrocarbons were formerly called *terpenes*, while their oxygenated derivatives were termed *camphors*; at present, they are together referred to as terpenoids.

The empirical composition suggested to Wallach that the terpene hydrocarbons were probably built up of isoprene units. This is the "isoprene rule" The suggestion has been partly substantiated by further analytical and synthetic evidence. Tilden showed that the pyrolysis of oil of turpentine gives isoprene; also rubber, on dry distillation yields isoprene. Synthetically, Bouchardt showed that isoprene can be dimerised to dipentene, by heating it to 280°C ; the latter is a typical terpene, widely distributed in nature. Lastly, it has been shown by Tilden and Harries that isoprene can be polymerised to a rubber-like product. The isoprene rule has been a useful guide but should not be regarded as a fixed rule. Usually a plant terpenoid will have a structure that would be divisible into isoprene units According to Ingold, these units in the natural terpenes are joined "head to tail" (the branched end of the isoprene molecule is regarded as the "head") the structural skeletones i.e. open chain struture of the monoterpenes are thus represented :—



The cyclic structures are derived from the above by suitable closing up of the chain. The isoprene rule can also be very useful in evolving a probable constitution of a natural terpenoid. Thus selinene, on dehydrogenation with selenium gives eudalene. The reaction establishes the position of all but one C atom. The isoprene rule helps indicate that the C atom is present as an angular methyl group at a definite position in the molecule.

CLASSIFICATION AND NOMENCLATURE:—A classification of the terpenes based on the number of C_5H_8 units present in the molecule

has been evolved. According to this the following fundamental types of terpenes with their composition are recognised.

(*i*) Hemi-terpenes C_5H_8 (These do not occur in nature.),

(*ii*) Mono-terpenes of terpenes $C_{10}H_{16}$ (most common),

(*iii*) Sesqui-terpenes $C_{15}H_{24}$ (less common),

(*iv*) Di-terpenes $C_{20}H_{32}$,

(*v*) Tri-terpenes $C_{30}H_{48}$,

(*vi*) Poly-terpenes $(C_5H_8)x$ (Resins and rubber).

The most important of the natural terpenes are the *mono* terpenes with the composition $C_{10}H_{16}$ *i.e.*, built up of two isoprene units. They are related to *p*-menthane ; they are subdivided into :—

(*a*) MONOCYCLIC-TERPENES :—These contain one cyclic system and two double bonds.

(*b*) DICYCLIC TERPENES :—These contain two cyclic systems and one double bond.

(*c*) OLEFINIC OR OPEN CHAINS TERPENES :—They possess an open chain structure and three double bonds.

Of all the three systems, the monocyclic system is the most important.

All these systems are closely related to one another ; both the dicyclic and non-cyclic systems can be smoothly converted into the monocyclic system. Among these, we have members belonging to the following fundamental types such as, hydrocarbons, alcohols, aldehydes, ketones atc.

METHODS OF ISOLATION : The majority of the essential oils are highly complex mixtures of compounds which are closely related to one another. The extraction of these oils from the tissues of the different plants is a big industry in many parts of the world. Various methods based on different principles have been developed from time to time to meet the requirements of a particular plant or a particular place of cultivation of the plant. The following are the most important ones :—

(*i*) STEAM DISTILLATION :—This method is applicable to many of the essential oils : lavender and rose oils are obtained in this way. This method, however, has some disadvantages. Some of the constituents of the natural oil may be esters, which are responsible

for the specific fragrance of the product. The esters may be hydrolysed by steam and thus the quality of the perfume may suffer accordingly. The method, however, is cheap.

(*ii*) Extraction with fat or lard and subsequent extraction with alcohol :—This method is widely known as the 'enfleurage' method and widely used in South of France. A large number of oils like rose and jasmine have been obtained in this way. It is claimed that this method gives higher yield of the oils. In a recent modification of this process, the natural oils are adsorbed by activated cocoanut charcoal. They are then removed from the charcoal by submitting the charcoal to steam. This method has three advantages over the old enfleurage method: (1) the activated charcoal can make much more contact with the flower petals than the lard or the grease; hence the extraction is more quantitative; (2) the charcoal is chemically more stable, while grease is likely to go rancid, with disastrous effects on the odour of the floral perfume; (3) the essential oils obtained by this method are free from glycerides which are extracted by the alcohol along with the perfumes, in the enfleurage method.

(*iii*) Extraction with special solvents; the most commonly used are ligroin, alcohol, ether and chloroform. This method gives a purer sample of the oil but the yields are not usually good.

The oil obtained by any one of the above methods is essentially a highly complex mixture of closely related compounds. This is subjected to fractional distillation: terpenes distil over first, followed by oxygenated derivatives. The residue on distillation under reduced pressure gives the sesquiterpenes, further separated by fractional distillation. The isolation of a pure terpene from such a mixture was further complicated by the observation that many terpenes readily undergo isomeric changes involving structural alterations like (*a*) change in the size of the ring, (*b*) shifting of the double bond and (c) ring closure in the presence of mineral acids or other usual reagents. However, the introduction of nitrosyl chloride $NOCl$ in 1877 by Tilden, enabled considerable progress to be made. The terpenes combine with this reagent additively, to form in many cases, crystalline products with a sharp melting-point and which could be used in the separation and identification of a terpene. The influence of the discovery of this reagent on terpene chemistry is only paralleled by that of phenyl-hydrazine on the development of sugar chemistry.

The nitroso-chlorides were first prepared by Tilden by the direct action of nitrosyl-chloride on a terpene in chloroform solution. But now they are usually obtained by the Wallach method in which the terpene is treated with a mixture of amyl nitrite or ethyl nitrite or butyl nitrite in glacial acetic acid and fuming hydrochloric acid.

GENERAL METHODS OF INVESTIGATION OF STRUCTURE IN THE TERPENE CHEMISTRY: A large amount of research work has been carried out to unravel the complicated structural relationships existing between the terpenes and camphors. The chief names connected with these fundamental researches are those of Wallach, Baeyer, Perkin, Semmler, Simonsen etc. The main types of reactions employed by them in the elucidation of the structure of terpenes can be grouped under two heads :—

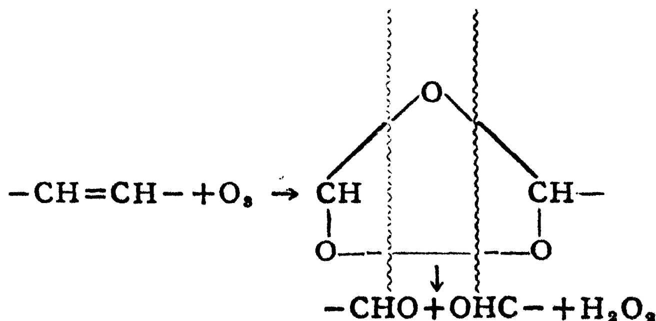
(*a*) analytical methods and (*b*) synthetical methods.

Analytical methods :—The chief of these include :—

(*a*) oxidation, (*b*) addition reactions,
(*c*) dehydration, (*d*) dehydrogenation.

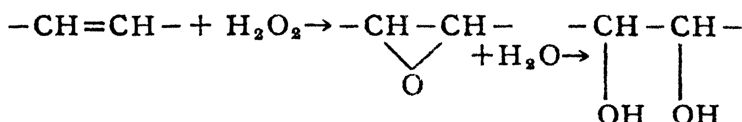
OXIDATION :—The oxidation methods have been very fruitful in the elucidation of the structure of the terpenes; especially the ozonisation studies have been of immense value. Oxidation of the terpene is effected by one of the following agents: ozone, hydrogen peroxide, potassium permanganate in alkaline and acid conditions, and nitric acid.

OZONE :—It reacts with the double bond to give an ozonide which on hydrolysis forms an aldehyde, ketone or acid depending on the original structure of the terpene. Schematically—



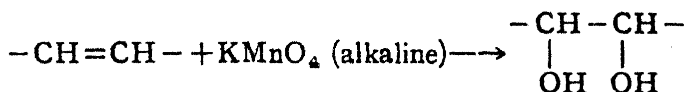
The molecule is oxidised and split up at the position of the double bond. The products of ozonolysis can thus be used to determine the structure of an unknown complex terpene. *cf.* ozonolysis of citral (q. v.). Recently the ozonide is hydrogenated catalytically with Pd/C and H_2 when a mixture of aldehydes and ketones is formed. The decomposition is also smooth. Ozone is a reagent of great analytical importance because it can be employed to detect, estimate and locate the unsaturation present in the molecule of a terpene. An additional advantage is that under the experimental conditions employed, the isomeric changes involving structural alterations, to which the terpenes as a class are prone are completely excluded.

HYDROGEN PEROXIDE:—The double bond if present in the molecule is attacked and converted into a glycol.

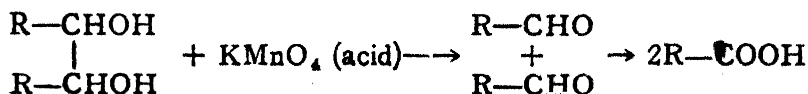


The formation of a glycol is used to detect the presence of the double bond. The glycol can be further oxidised to a mixture of aldehydes and acids which can be readily identified.

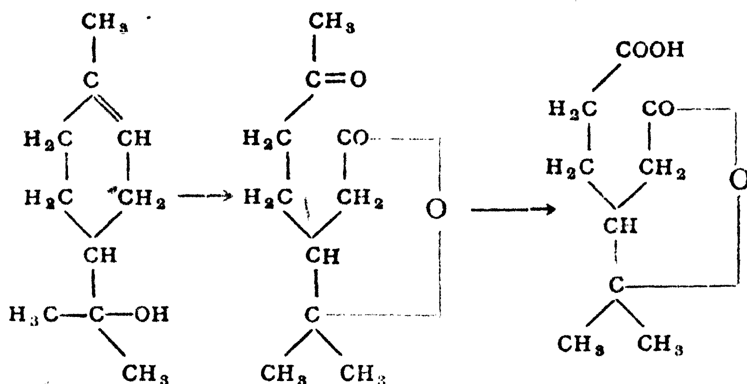
POTASSIUM PERMANGANATE:—This reagent is used under alkaline and acid conditions and thus can effect the oxidation of the terpene in definite stages. The products of such stepwise oxidation have been isolated and are of great importance in arriving at the structure of the terpene molecule. In the case of the monocyclic terpenes, a dibasic acid, usually the terephthalic acid is formed. It is such oxidation reactions as in the case of terpineol that have proved very fruitful in the elucidation of the structure of the molecule:—



On further oxidation, the glycol is decomposed and converted into an aldehyde or acid.



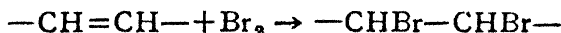
The cleavage of the molecule takes place at the position originally occupied by the double bond. *cf.* the disintegration of the terpineol molecule (graded oxidation).



NITRIC ACID :—Oxidation of a terpene with concentrated nitric acid is usually a very drastic reaction. The terpene molecule is disintegrated into simple aliphatic and aromatic acids. Camphor is converted into camphoric and camphoronic acids by the action of concentrated nitric acid.

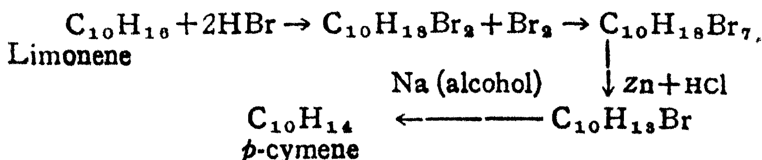
ADDITION REACTIONS :—As the terpenes are unsaturated compounds, they readily combine with a number of reagents additively. The most commonly used reagents are :

(*i*) Halogens : (chiefly chlorine and bromine) ; The terpenes give di-or tetra-halogen derivatives. The reaction therefore can be used to determine the amount of unsaturation in the molecule.



$$-CH{=}CH- + Br_2 \rightarrow -CHBr-CHBr-$$

Baeyer and Villiger have employed the method of *exhaustive bromination* to determine the nature of the carbon skeleton present in a terpene molecule. The terpene is treated with excess of bromine and the bromo derivative is reduced with zinc and hydrochloric acid, and subsequently with sodium and alcohol. In this process the alkyl radicals if present are left undisturbed. Limonene is thus converted into *p*-cymene :—



$$\underset{\text{Limonene}}{C_{10}H_{16}} + 2HBr \rightarrow C_{10}H_{18}Br_2 + Br_2 \rightarrow C_{10}H_{18}Br_7$$

$$\downarrow Zn + HCl$$

$$\underset{p\text{-cymene}}{C_{10}H_{14}} \xleftarrow{\text{Na (alcohol)}} C_{10}H_{18}Br$$

(*ii*) Halogen acids like HCl or HBr : with terpenes, the addition of the halogen acid, takes place smoothly and the products are usually crystalline and often serve for the identification of the terpenes. The terpene is dissolved in a suitable solvent like acetic acid and dry halogen acid is passed into the solution. Limonene thus gives a crystalline bis-hydrochloride.



$$C_{10}H_{16} + 2HCl \longrightarrow C_{10}H_{16}\cdot 2HCl$$

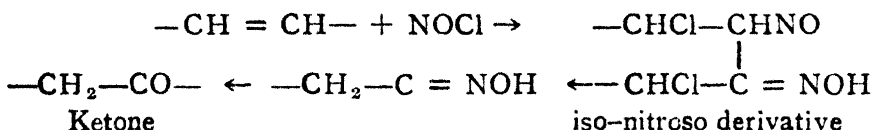
The addition of the halogen acid, is in accordance with the Markownikoff's rule. If the double bond lies between two carbon atoms one of which is tertiary, the halogen atom attaches itself to the latter :—



$$(CH_3)_2C = CH{-}CH_3 \xrightarrow{HBr} (CH_3)_2C.Br{-}CH_2{-}CH_3$$

(*iii*) Nitrosyl chloride *NOCl*, and oxides of nitrogen, NO_2 and N_2O_3 :— Nitrosyl chloride reacts readily with the double bond of the terpenes to form additive compounds. These addition products are of great significance in the terpene chemistry because :

(*a*) they are usually crystalline compounds with sharp melting-points and hence can be used for the separation and identification of the terpenes, and (*b*) they can be made to undergo an important series of reactions.



$$-CH = CH- + NOCl \rightarrow \quad -CHCl{-}CHNO$$

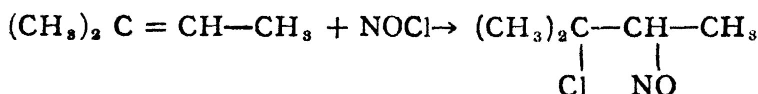
$$-CH_2{-}CO- \leftarrow -CH_2{-}C = NOH \longleftarrow -CHCl{-}C = NOH$$

Ketone — iso–nitroso derivative

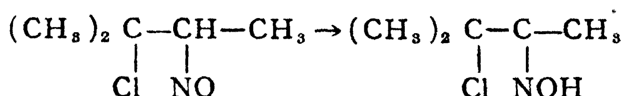
The compounds so obtained are ketonic derivatives and extremely reactive and capable of undergoing numerous transformation reactions and thus serve for the elucidation of the structure of the molecule. The intermediately formed oximes have also found important and synthetical and analytical applications. *cf*. the conversion of dipentene or terpineol into carvone (q. v.).

The addition of nitrosyl chloride to the terpene molecule can take place in two ways : (*a*) If the double bond lies between two tertiary carbon atoms, the chlorine atom attaches itself to one carbon atom and the *NO* to the other, giving rise to ***blue*** nitroso-derivatives. This fact has been utilised for locating the double bonds in a terpene molecule since the 4–8 position is the only one in which a double

bond can be tetra-substituted (*i.e.* ditertiary) in the *p*-menthane skeleton. (*b*) If, however, the double bond lies between two carbon atoms, one of which is secondary and the other tertiary, the chlorine atom attaches itself to the tertiary carbon atom and the nitroso group to the secondary.

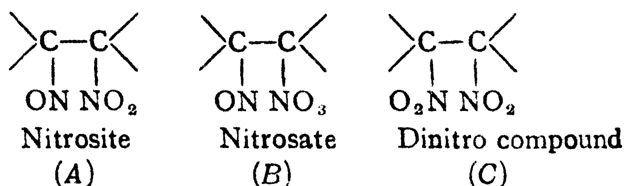


The nitroso-derivative so formed then isomerises to the oxime which is colourless.

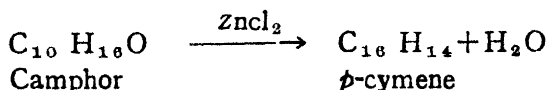


Sometimes, the nitroso derivative suffers polymerisation to dimeric forms which are also colourless.

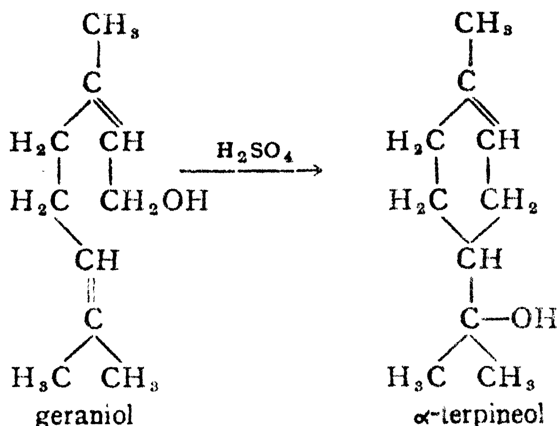
The terpenes also combine with nitrogen-trioxide to form nitrosites (*A*). With nitrogen tetroxide the corresponding nitrosates (*B*) and dinitroderivatives (*C*) are obtained.



(*c*) Dehydration:—Oxygenated terpenes, the alcohols and ketones readily lose a molecule of water under the action of a dehydrating agent and are transformed into simple aromatic dervatives. Thus we have:—



The dehydrating agents most commonly used are: phosphorus pentoxide, potassium hydrogen sulphate, anhydrous zinc chloride and glacial acetic acid in concentrated sulphuric acid. The olefinic terpenes are converted by these reagents into monocyclic terpenes, *e.g.*, geraniol is converted into α-terpineol by the action of sulphuric acid.



geraniol α-terpineol

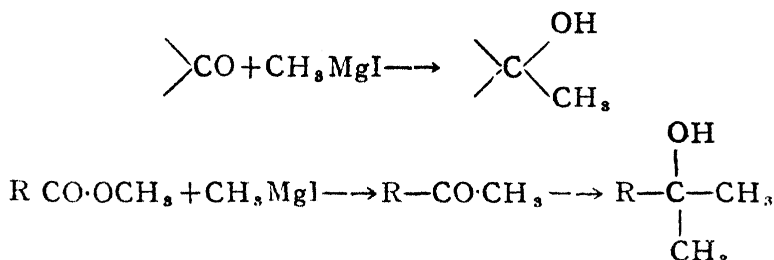
Both dehydration to form the ring and subsequent hydration of the double bond to give the tertiary alcohol are probably involved here.

(*iv*) DEHYDROGENATION :—This is usually effected by heating the terpenes with zinc, iodine, bromine, or sulphur. The terpene is converted with loss of hydrogen into aromatic compounds; usually the product is *p*-cymene in the case of mono and dicyclic terpenes. Turpentine and camphor are, in this way, converted into *p*-cymene. Recently, use of selenium has been recommended by Vesterberg. Dehydrogenation by means of selenium has been of special practical importance in the conversion of cyclo-hexane derivatives into the more easily identifiable aromatic compounds. The excess of hydrogen is eliminated as hydrogen selenide, very readily and smoothly, while selenium unlike sulphur shows no tendency to combine with the aromatic compounds formed.

We shall now turn to the *synthetic methods* that have proved fruitful in the elucidation of structural relationships among the terpenes.

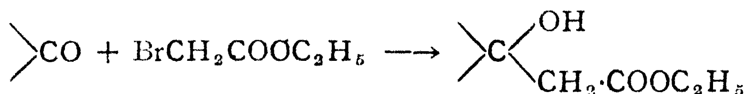
(*i*) SABATIER AND SENDEREN'S METHOD: CATALYTIC HYDROGENATION METHOD: (Molecular H_2 in presence of Ni) By this method, the aromatic compound is converted into the hydromatic compound. Thus it is possible to obtain synthetically hydroaromatic derivatives *i.e.* terpenes containing suitable groups from the corresponding aromatic compounds. Thymol, an aromatic compound is readily reduced to menthol a terpene alcohol.

(*ii*) THE GRIGNARD REACTION:—It is employed with great success by Perkin and his school, to synthesise a number of the naturally occurring terpenes or compounds directly related to them. With the help of this reagent methyl or isopropyl groups, which are so common in the natural terpenes can be readily introduced into a compound containing a carbonyl group.

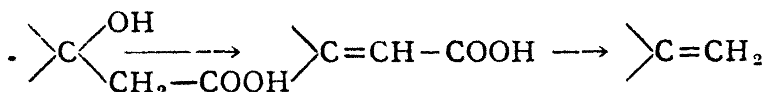


Tertiary alcohols are thus readily obtained. The natural terpene, α-terpineol is such a tertiary alcohol. It has been synthesised by a direct application of this reaction.

(*iii*) REFORMATSKY'S REACTION:—This reaction also has been of great help to synthesise such compounds as camphoronic acid, geranic acid, etc. These syntheses have definitely established the structural relationships of many a natural terpene. The reaction consists in the action of an α-halogen substituted ester of a fatty acid on a ketone in presence of Zn in ether or benzene solution.



A β-hydroxy acid is thus produced which may be further converted into an unsaturated acid or a hydrocarbon:

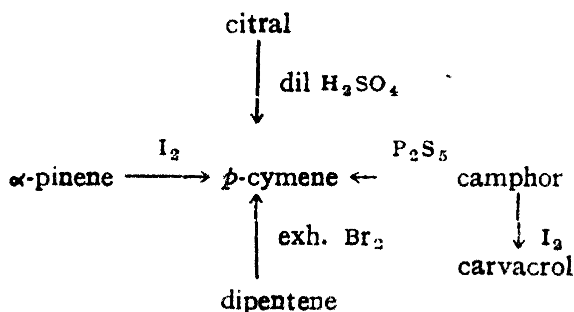


All the above reactions have found fruitful applications in the terpene chemistry.

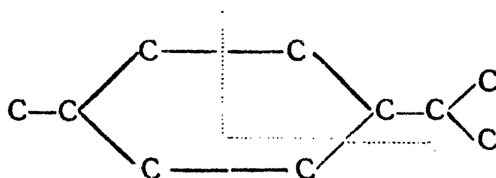
A number of physical methods have been also used in the elucidation of the structures of the natural terpenoids. The important ones include the determination of (i) refractive index (ii) optical activity (iii) the absorption spectra the U. V. and the infra red. These serve to confirm the structures established by the chemical methods.

MONOCYCLIC TERPENES AND COMPHORS

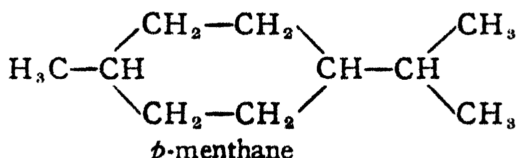
The most common and widely distributed terpenes in nature belong to this group. Majority of them are derived from and related to *p*-cymene, which is purely aromatic compound, and is of very common occurrence. The above relationship is revealed by studies in oxidation behaviour of the terpenes, and by other reactions. Thus, on oxidation, they give *p*-toluic acid and terephthalic acid. Also, many terpenes and camphor, can be readily converted into *p*-cymene or into thymol or into carvacrol which are the hydroxy derivatives of *p*-cymene;



The *p*-cymene molecule contains the following C-skeleton:



which contains two isoprene units. It is thus obvious that the monocyclic terpenes are built up of two isoprene units; this is in agreement with the isoprene rule. The saturated hydrocarbon corresponding to the above skeleton will be:—

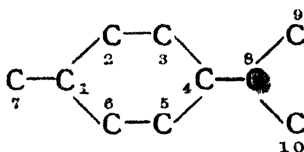


p-menthane

It is hexahydro-*p*-cymene and has the molecular composition $C_{10}H_{20}$. Wagner called it menthane and the terpenes $C_{10}H_{16}$ which represent the corresponding unsaturated hydrocarbons were called

menthadienes. Baeyer had proposed the names *terpane* and *terpadienes* respectively; *p*-menthane does not occur in nature, but it has been synthetically obtained by the catalytic hydrogenation of *p*-cymene. It is a liquid b.p. 170°.

All the terpenes of monocyclic system can be regarded as derived from this parent hydrocarbon. The carbon atoms are numbered as given below and the position of the alkyl radicals and the double bonds are indicated by the corresponding number:—

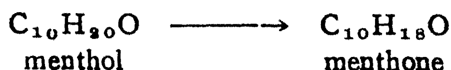


The number of possible isomers in the case of menthadiens is fourteen only. A double bond between carbon atoms 1 and 2 is indicated by the symbol Δ^1. The natural products are then found to belong to one of the following sub-groups:— (*a*) Menthanes: saturated systems. (*b*) Menthenes: mono-unsaturated systems. (*c*) Menthadienes : di-unsaturated systems. A few natural products are known which are derived from the isomeric m-cymene (m-menthane series).

Menthane Group

The most common and important essential oils, belonging to this group are : menthol, menthone and ∝-terpineol ; the chemistry of these compounds will be discussed below.

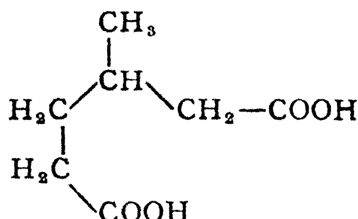
Menthol is the chief constituent of oil of peppermint. It is *l*-rotatory. It melts at 43°C and possesses a strong smell of preppermint. It finds use as an anesthetic and antiseptic. The structural formula for menthol is based on that of menthone to which it is very closely related. Menthol has the composition $C_{10}H_{20}O$. On oxidation it forms a ketone $C_{10}H_{18}O$ called menthone ; it is a liquid b.p. 207°C.



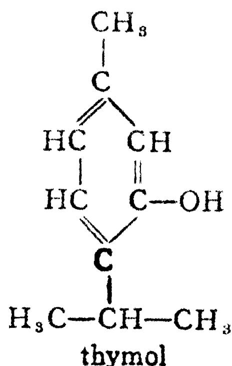
$$\underset{\text{menthol}}{C_{10}H_{20}O} \longrightarrow \underset{\text{menthone}}{C_{10}H_{18}O}$$

Menthol, therefore, carries a secondary alcoholic (*CHOH*) group. The nature of carbon frame-work is revealed by the decomposition reactions of menthone. Menthone on oxidation with potassium

permanganate, gives keto-menthylic acid which on further oxidation gives β-methyladipic acid. The latter has the structure :—

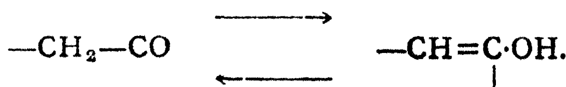


But it is only a cyclic ketone that would give a dibasic acid on oxidation ; (the other possibility of an unsaturated compound giving a dibasic acid does not apply here), hence menthone must contain a ring system. This is confirmed by other behaviour of menthone. Thus on bromination, menthone gives a dibromoderivative $C_{10}H_{16}B_2O$, which when heated with quinoline is converted into thymol $C_{10}H_{14}O$; the latter has the structure :

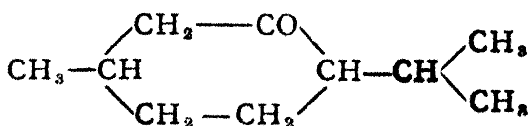


thymol

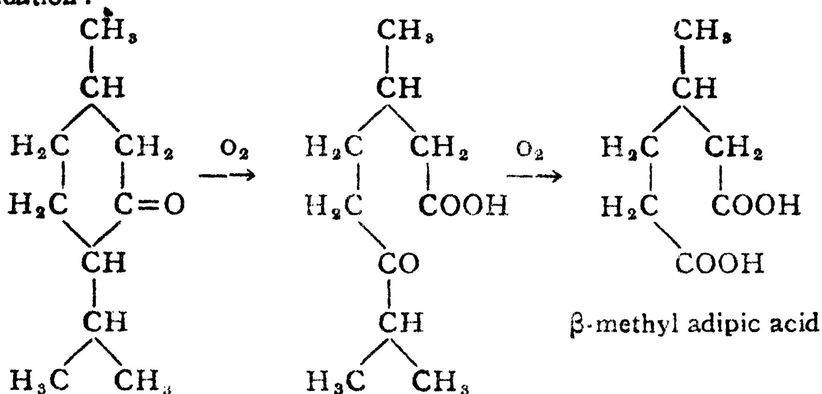
The elimination of hydrobromic acid under the influence of quinoline which converts a hydroaromatic system into an aromatic one is also accompanied by enolisation :—



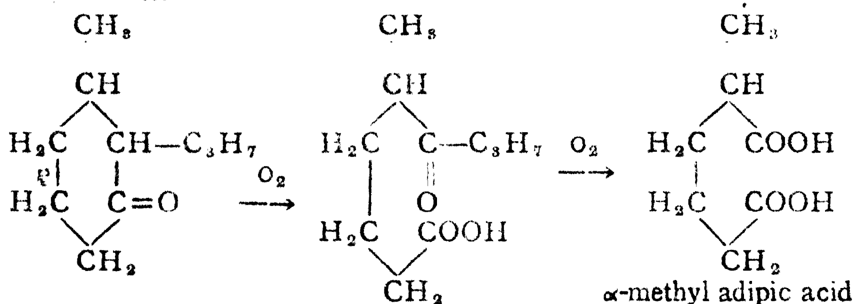
This also establishes that the carbonyl group of menthone and hence the secondary alcoholic group of menthol is in position 3 or *meta* to the methyl group. Menthone, therefore, must be represented by :—



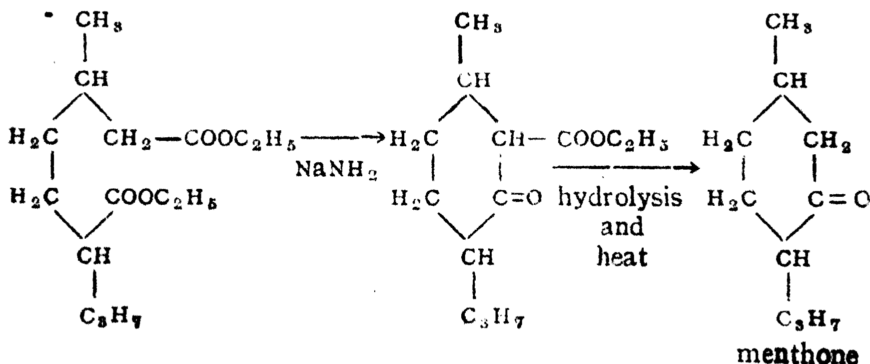
That the methyl and isopropyl groups are in para position to each other is indicated by the formation of β-methyl adipic acid on oxidation :—



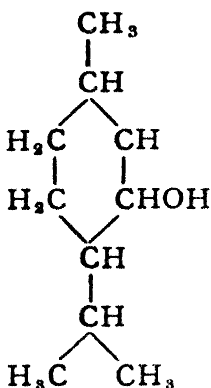
If the methyl group were present in any other position, the product of decomposition would be α-methyl adipic acid instead of the β-isomer.



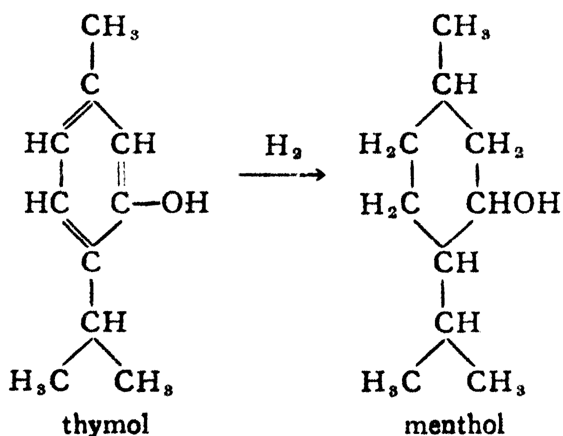
The structure is finally confirmed by a synthesis ; β-methyl-α isopropyl pimelic ester is made to undergo intra-molecular condensation in presence of sodamide (Dieckmann).



Haller and Martine have also achieved a synthesis of menthone starting from 3 methyl-cyclo-hexanone, which is converted into menthone by the action of isorpropyl-iodide in presence of sodamide. Menthone on reduction with sodium and alcohol gives menthol. Hence menthol is :—

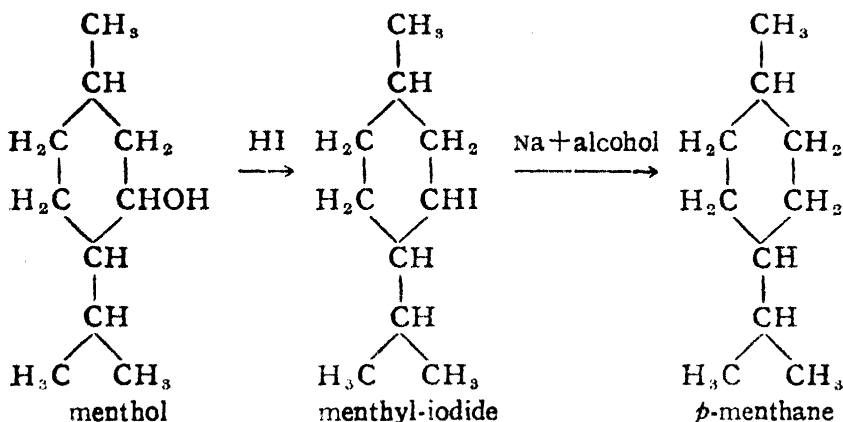


This is confirmed by the synthesis of menthol from thymol by catalytic hydrogenation :



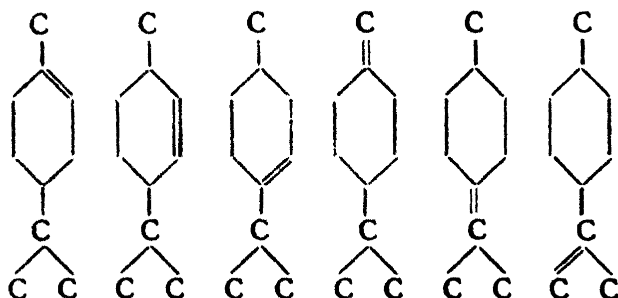
thymol menthol

RELATION TO *p*-MENTHANE :—Menthol on treatment with hydriodic acid, forms menthyl iodide which on reduction with sodium and alcohol yields *p*-menthane :—



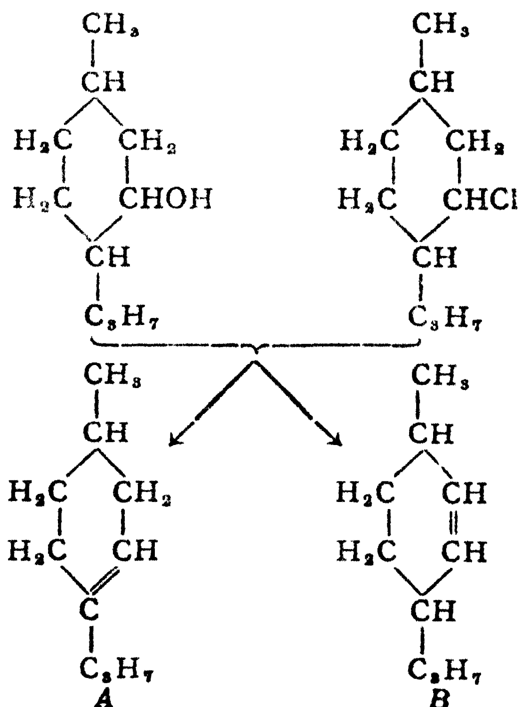
Menthol is now obtained by the catalytic hydrogenation of thymol which is synthesised from *m*–cresol and iso–propyl alcohol in presence of con. H_2SO_4. Menthone is then prepared by oxidation of menthol with $K_2Cr_2O_7$ in acid solution.

MENTHENE or Δ^3 menthene is the most important member of the menthenes *i. e.* the unsaturated hydrocarbons with one double bond, derived from *p*–menthane. The formulas for six possible menthenes are :

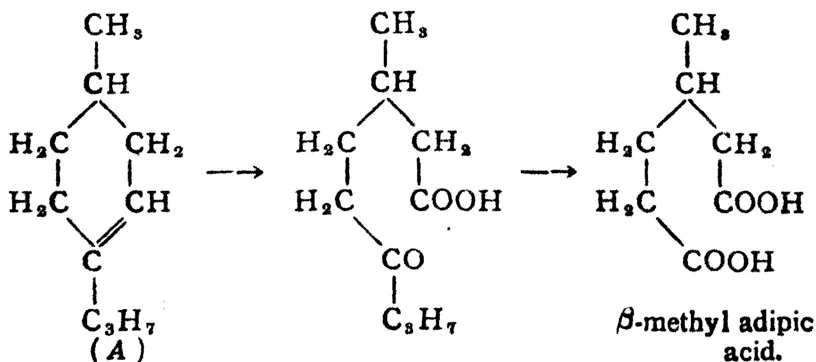


Menthene is a constituent of oil of thyme. It is closely related to menthol from which it can be readily obtained. Thus menthol on dehydration gives menthene; or menthene can be obtained from menthyl chloride by elimination of one molecule of hydrochloric acid.

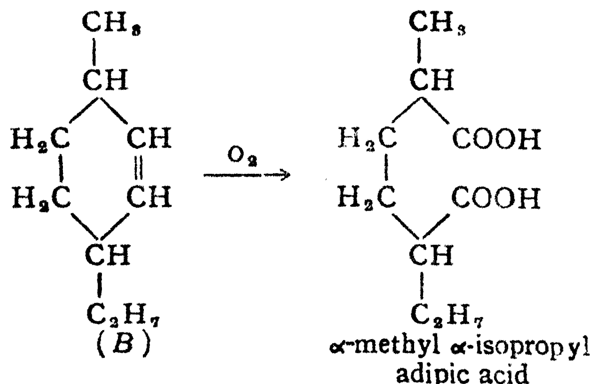
But the elimination of water from menthol or hydrochloric acid from menthyl chloride may take place in two ways :—



That the menthene from oil of thyme, possesses the structure *A* is indicated by the results of oxidation. On oxidation with potasium permanganate, it is converted into *β*-methyl adipic acid —



While α-methyl α-isopropyl adipic acid would result from (*B*).

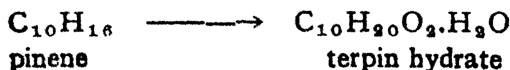


Hence the structural formula for menthene is (*A*). The difference between the two formulas is in the position of the double bond and the choice between the two alternative formulas is made by a study of oxidation products.

α - Terpineol

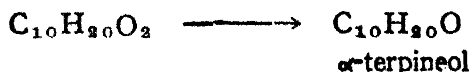
α-Terpineol is the alcohol of menthene series. It is present in many essential oils like cardamom oil, marjoram oil and cajeput oil. It has the pleasant smell of lilacs. It is a solid m.p. 35° (b.p. 219°). It is one of the most important members of the monocyclic terpenes, because it is related to a large number of such terpenes; it can be readily converted into other terpenes, *e.g.* dipentene, terpinene, terpinolene etc. Also a large number of natural terpenes can be transformed into terpineol. Hence a study of the structure of terpineol is of great importance in determining the structure of the other terpenes related to it.

Commercially, α-terpineol is obtained by boiling pinene, with dilute sulphuric acid in acetic acid solution, when terpin hydrate is first formed;



$$\underset{\text{pinene}}{C_{10}H_{16}} \longrightarrow \underset{\text{terpin hydrate}}{C_{10}H_{20}O_2.H_2O}$$

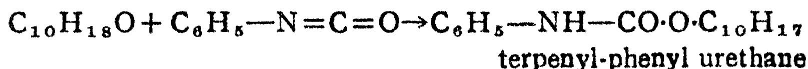
the latter, on dehydration with H_3PO_4 gives α-terpineol.



$$C_{10}H_{20}O_2 \longrightarrow \underset{\alpha\text{-terpineol}}{C_{10}H_{20}O}$$

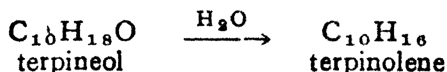
Constitution : It has the molecular composition $C_{10}H_{18}O$, and gives the following reactions:

α-Terpineol reacts with phenyl-iso-cyanate $C_6H_5N=C=O$ to form the corresponding urethane, m.p. 112°C.



$$C_{10}H_{18}O + C_6H_5—N=C=O \rightarrow C_6H_5—NH—CO·O·C_{10}H_{17}$$
terpenyl-phenyl urethane

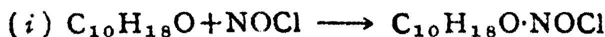
The presence of a hydroxyl group is thus indicated and as the compound is insoluble in sodium hydroxide, the hydroxyl group cannot be a phenolic one. Further, that it is a tertiary alcoholic group is proved by the ease with which terpineol suffers dehydration when heated with sulphuric acid in glacial acetic acid.



$$\underset{\text{terpineol}}{C_{10}H_{18}O} \xrightarrow{H_2O} \underset{\text{terpinolene}}{C_{10}H_{16}}$$

N.B.—Dipentene is formed, when $KHSO_4$ is used as the dehydrating agent.

NATURE OF UNSATURATION AND OF THE CARBON FRAMEWORK PRESENT IN THE MOLECULE: (*a*) α-Terpineo combines readily with one melecule of nitrosyl chloride on of bromine :—



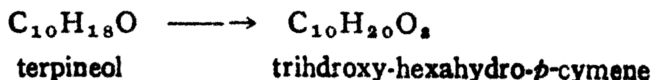
(*i*) $C_{10}H_{18}O + NOCl \longrightarrow C_{10}H_{18}O·NOCl$



(*ii*) $C_{10}H_{18}O + Br_2 \longrightarrow C_{10}H_{18}O·Br_2$

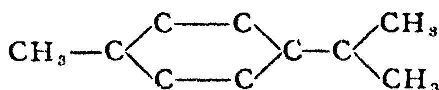
α-Terpineol therefore contains one double bond. The molecular composition in $C_{10}H_{18}O$; a saturated open chain compound should have the composition $C_{10}H_{22}O$ and there is only one double bond; hence there must be one ring in the molecule. The position of the double bond and the nature of the ring are established by the studies of oxidative degradation of the molecule.

Wallach has carried out a systematic investigation of the decomposition products of terpineol when oxidised under different conditions. It is these researches that have furnished the key to the structure, of the compound. [Wallach obtained as the first oxidation product, with dilute aqaeous potassium permanganate, a compound which is tri-hydroxy-hexahydro-*p*-cymene.]



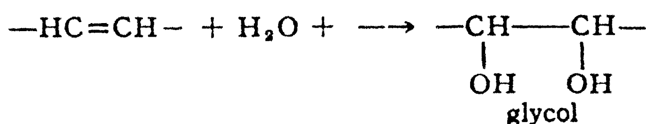
$$\underset{\text{terpineol}}{C_{10}H_{18}O} \longrightarrow \underset{\text{trihdroxy-hexahydro-}p\text{-cymene}}{C_{10}H_{20}O_3}$$

The carbon frame-work in the molecule is therefore the same as is present in *p*-cymene :



This confirms the presence of six-membered ring in the molecule.

Further, there are three hydroxyl groups in the oxidation product, one of which was originally present and the other two are added during the oxidation, at the place of the double bond. This is in accordance with Wagner's rule which states that the first step in the oxidation of a compound containing a double bond is the formation of a glycol, by the addition of a hydroxyl group each of the carbon atoms linked by the double bond :—



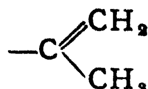
The exact poshition of the double bond is revealed by the results of further oxidation studies. The trihydroxy compound has the same number of carbon atoms as the original compound and on further oxidation is converted into a substance containing the same number of carbon atoms $C_{10}H_{16}O_3$; it is neutral but dissolves in alkali, on warming and on back titration found to consume one equivalent of alkali ; hence it has to be a lactone ; and as it is stable, it must be a γ lactone and further it forms a semicarbazone and gives acetic acid on oxidation. The formation of acetic acid on oxidation, is characteristic of methyl ketones.



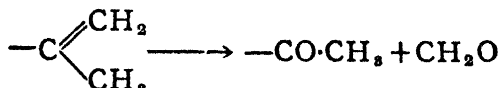
Therefore, the oxidation product $C_{10}H_{18}O_6$ contains a —CO·CH_3 group.

As the oxidation takes place at the point of the original double bond, it follows that the latter must be present on a carbon atom, carrying also CH_3 group. The molecule of α-terpineol as established above contains a ring and side chains. Hence the double bond may be present in the ring or in one of the side chains. If the double

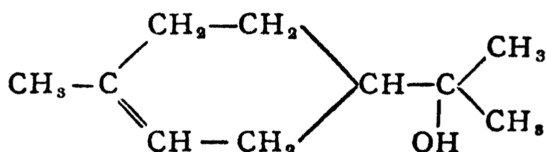
bond were present in a side chain, the molecule would carry the grouping :



The formation of a methyl ketonic derivative, in this case, will be accompanied by the elimination of one carbon atom ;



which, however, is not the case. Hence the double bond cannot be present in the side chains. Further, as the oxidation product is a methyl ketone, the double bond must be present in the ring on the C atom carrying the CH_3 group. Hence the probable formula :



This formulation is in complete accord with the results of graded oxidation.

The keto lactone on further oxidation with potassium permanganate is changed into homoterpenylic acid, which can be further oxidised to terpenylic acid, and finally to terebic acid, with CrO_3 in acetic acid. The changes in composition involved in these degradations starting form α-terpineol are as follows :—

α-terpineol → tri-hydroxy menthane → keto-lactone

$C_{10}H_{18}O$ $C_{10}H_{20}O_3$ $C_{10}H_{16}O_3$ or $C_8H_{13}O_2{\cdot}COCH_3$

↓

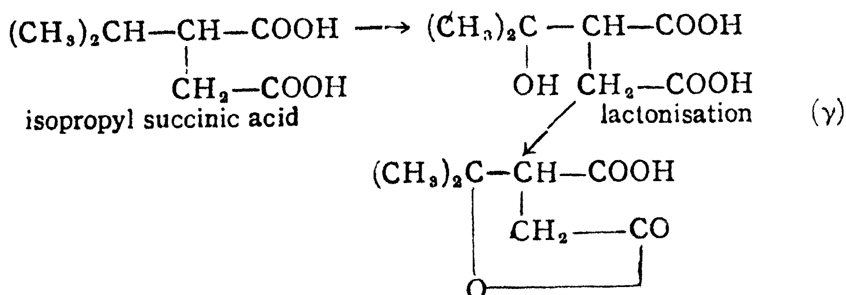
terebic acid ⟵ terpenylic acid ⟵ homoterpenylic acid

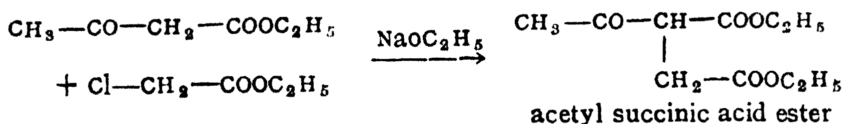
$C_6H_9O_2{\cdot}COOH$ $C_7H_{11}O_2{\cdot}COOH$ $C_8H_{13}O_2{\cdot}COOH$

The acids formed are lactonic in nature and differ in their composition by a CH_2 group. Hence they form a homologous series. It is obvious that the constitution of terpineol must be related to those of terebic and terpenylic acids etc. and directly derived from them. The structures of terebic and terpenylic acids have been established both by analytical and synthetical methods by Simonsen.

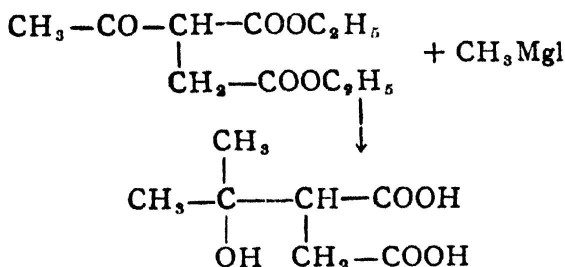
TEREBIC ACID :—It is obtained by the oxidation of isopropyl-succinic acid with chromic acid. It is a crystalline compound, m.p. 175°C.



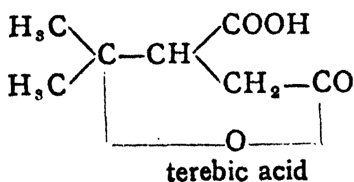
The above structure is confirmed by a synthesis by Simonsen. Acetyl-succinic acid is first obtained by the interaction between chloroacetic ester and ethyl-aceto acetate in the presence of sodium ethoxide :—



The ketonic ester is next treated with methyl magnesium iodide in ether, and subsequently hydrolysed with cold dil. mineral acid The ketonic carbonyl group is preferentially attacked.



which spontaneously passes into the lactonic acid, terebic acid :



terebic acid

Another synthesis of terebic acid starts from bromo succinic ester. The latter is condensed with acetone in presence of zinc (Reformatsky's reaction). Schematically :—

```
H3C\
    >CO + Zn + Br—CH—COOC2H5
H3C/             |
      |          CH2—COOC2H5
      ↓ hydrolysis
  H3C\
      >C—CH—COOH
  H3C/ |  |
       |  CH2——CO
       |        |
       |___O____|
     terebic acid
```

Now terpenylic acid which is the higher homologue of terebic acid will have the structure :—

```
H3C       /CH2—COOH
   \     /
    >C—CH
   /  |  \
H3C   |   \CH—CO
      |        |
      |____O___|
   terpenylic acid
```

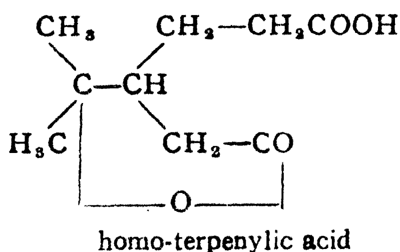
(Terpenylic acid is also obtained by oxidation of turpentine with chromic acid. It is a solid m.p. 90°).

This constitution for terpenylic acid is confirmed by a synthesis starting from β-acetyl *glutaric acid*, the next higher homologue of succinic acid (Simonsen), which is obtained from aceto acetic ester and chloroethyl acetate and $NaOC_2H_5$.

```
              /CH2—COOC2H5
             /
CH3—CO—CH            +CH3—Mg—I
             \
              \CH2—COOC2H5

        β-acetyl-gutaric ester
H3C           ↓ hydrolysis
   \          /CH2—COOH
    C—CH<
   /|         \CH2—CO
H3C |               |
    |______O________|
     terpenylic acid
```

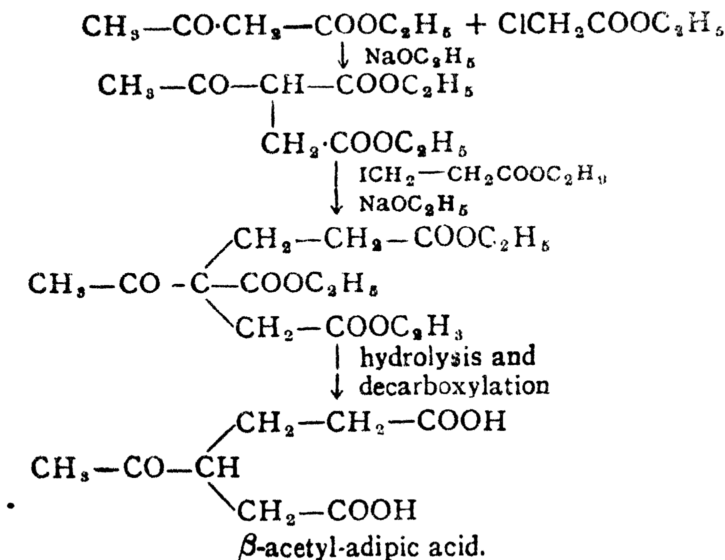
Homo-terpenylic acid which is the higher homologue of terpenylic acid would therefore be represented by :—



homo-terpenylic acid

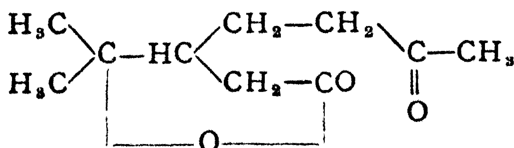
This structure can be further confirmed by an exactly analogous method, starting from β-acetyl *adipic acid,* (higher homologue of glutaric acid).

The latter is synthesised according to the following scheme :



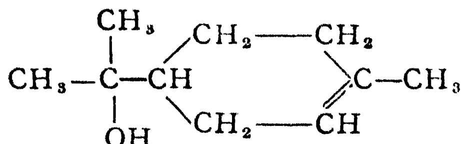
β-acetyl-adipic acid.

The structure of the methyl ketone follows from that of the homo-terpenylic acid which is formed from the ketone by replacement of the methyl ketonic group by *COOH* group. It is :



The methyl ketone is obtained by the oxidation of terpineol when the double bond is attacked.

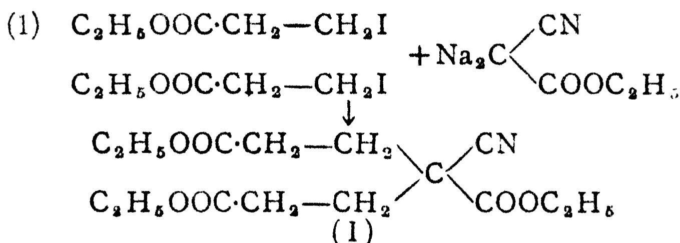
Now it can be shown that the formation of the above oxidation products (whose structures are established by synthesis) can be readily accounted for by the formula assigned to terpineol *viz.* (p 226).



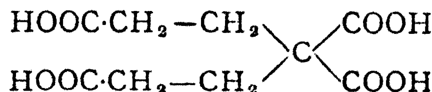
The oxidation of the molecule starts at the double bond, followed by cleavage at the same point. The disintegration of the molecule takes place stepwise and the process is referred to as "graded oxidation." The above structure has been confirmed by an elegant synthesis by Perkin.

SYNTHESIS OF α-TERPINEOL:—Perkin has accomplished a complete synthesis of α-terpineol. The various steps involved are:—

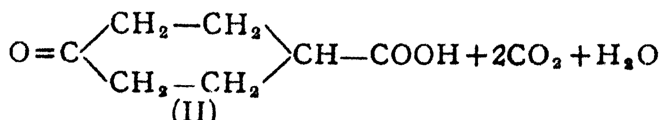
(*i*) Synthesis of keto hexa-hydro-benzoic acid: β-Iodo-propionic ester is treated with the di-sodium derivative of cyano-acetic-ester which is very reactive, at ordinary temperature, to form γ-cyano-pentane α, μ tri-carboxylic ester, in presence of $NaOC_2H_5$ in alcohol.



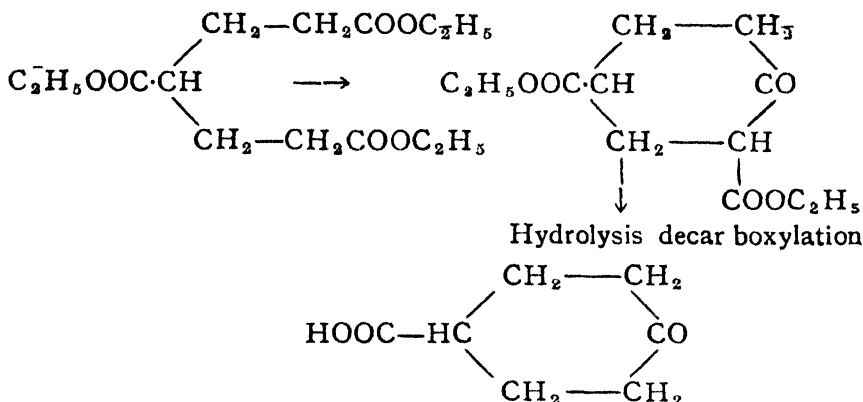
On hydrolysis with conc. hydrochloric acid, the corresponding free acid is formed.



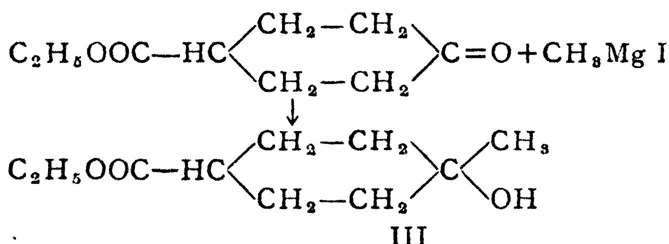
which on boiling with acetic anhydride and distillation, loses water and carbon dioxide to yield δ-keto-hexahydro-benzoic acid (II).



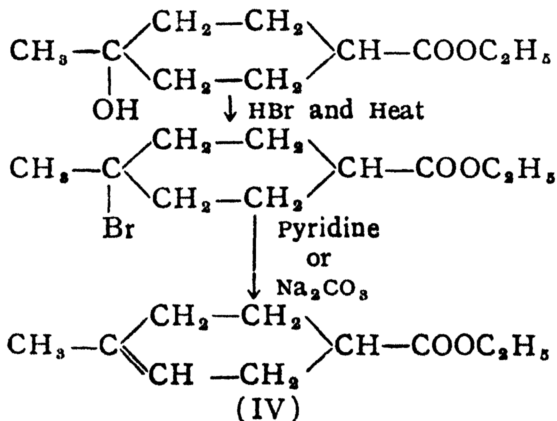
The δ-keto-hexahydro-benzoic acid can be obtained by an application of Dieckmann's reaction :



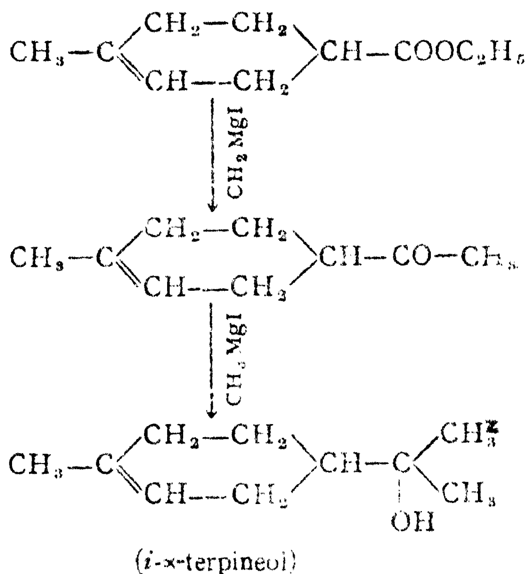
(*ii*) Conversion of the δ-keto-hexahydro-benzoic acid into α-terpineol. The ester of the acid is made to interact with methyl magnesium iodide, CH_3MgI. The keto group is attacked and δ-hydroxy-hexahydro-toluic ester (III) is formed :—



The hydroxyl group of this ester (III) is replaced by bromine by the action of fuming hydrobromic acid and subsequently a molecule of hydrobromic acid is eliminated by means of pyridine to give ester of Δ^3 tetra-hydro *p*-toluic acid (IV).

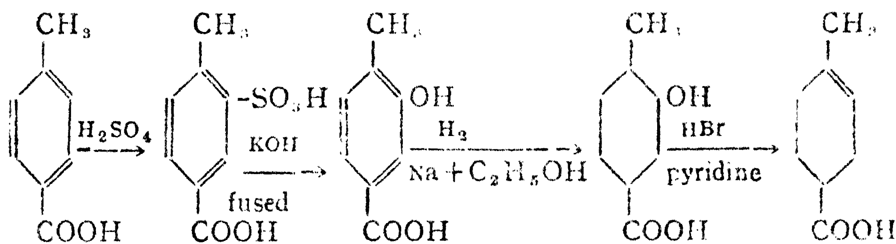


This ester (IV) is treated with excess of methyl magnesium iodide when the ester group is attacked and the product formed on hydrolysis, gives inactive terpineol :—



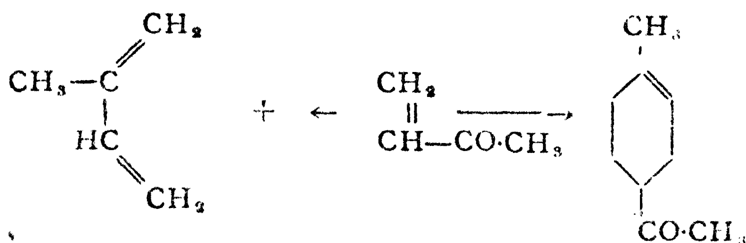
(*i*-α-terpineol)

The acid corresponding to the ester (IV) is synthesised starting from *p*-toluic acid.

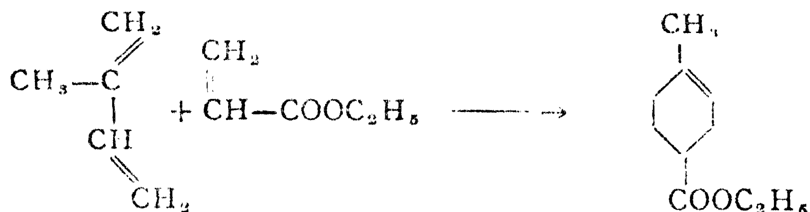


Fischer and Perkin have obtained optically active forms of α-terpineol. They resolved the intermediate acid corresponding to the ester (IV) into its optical active forms by one of the standard methods and converted the active form of the acid into the active terpineol.

Recently two more syntheses based on the Diel and Alder reaction have been reported. In one synthesis isoprene is condensed with methylvinyl ketone to 1 methyl Δ^1 cyclo hexenyl methyl ketone



the latter on treatment with CH_3MgBr and subsequent hydrolysis gives ∝-terpineol : the other is due to Alder and Vogt. They have synthesised the ester IV by a one step process ; isoprene is condensed with acrylic ester.



The latter can then be converted into ∝- terpineol as indicated earlier.

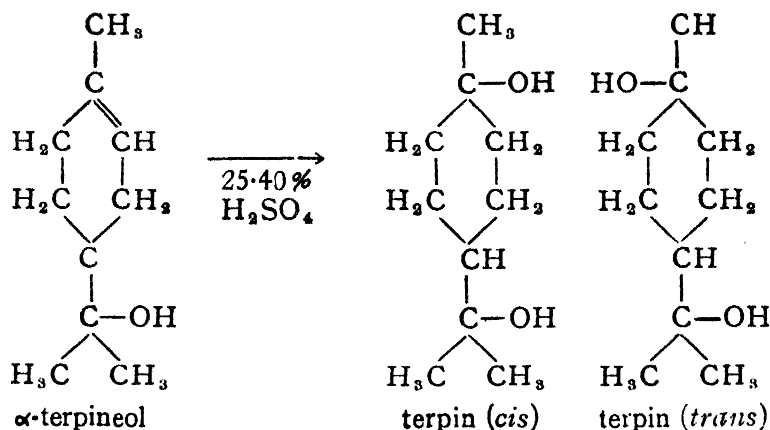
The following structural isomers of ∝-terpineol have been isolated. According to the system of nomenclature in the monocyclic series, ∝-terpineol is Δ^1 menthene 8-ol. Similarly we have :—

β- terpineol is $\Delta^{8(9)}$	menthene 7 ol
γ- terpineol is $\Delta^{4(8)}$	menthene 1 · ol
1- terpineol is Δ^8	menthene 1 · ol
4- terpineol is Δ^1	menthene 4 · ol

The commercial terpineol is a mixture of the isomers ∝, β, γ terpineol in which the ∝-isomer predominates.

• *Some typical reactions of ∝-terpineol :* ∝-Terpineol, because of the presence of a double bond and a tertiary alcholic group, is very reactive and suffers readily (i) oxidation, (ii) hydration and (*iii*) dehydration, and (*vi*) conversion to carvone. The oxidation reactions of the molecule have been already fully discussed, (see p. 216). The products of (*ii*) and (*iii*) and (*iv*) will be examined here in detail.

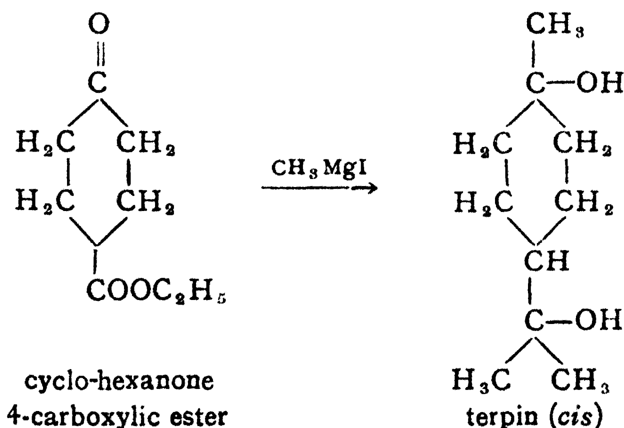
HYDRATION OF ∝-TERPINEOL :—On boiling with dilute sulphuric acid terpineol is hydrated and *terpin* is formed. Elements of water are added to the double bond and two isomeric products *cis* and *trans* are made possible. Thus we have :—



α-terpineol terpin (*cis*) terpin (*trans*)

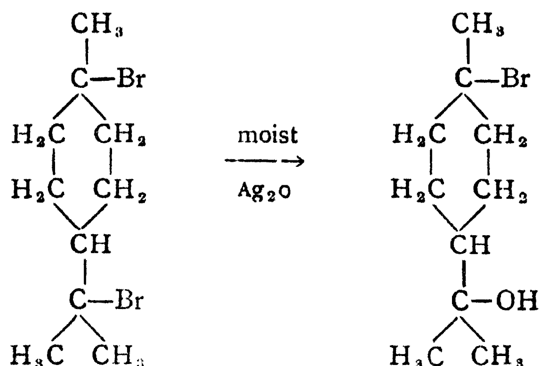
The terpin (now called terpinol) obtained from α-terpineol represents the *cis* form. This isomer is the more common. It readily combines with water to form a crystalline hydrate $C_{10}H_{20}O_2H_2O$. It melts at 104°. Its structure is confirmed by the following synthesis by Kay and Perkin.

Cyclo-hexanone 4-carboxylic ester is treated with methyl magnesium iodide in excess, in ether. Both the keto carbonyl group and the ester group are simultaneously attacked to give a di-hydric (di-tertiary) alcohol terpin (*cis*).



cyclo-hexanone 4-carboxylic ester terpin (*cis*)

Terpin (*cis*) is also obtained from 1-8 dibromo-menthane (from dipentene and hydrobromic acid) by the action of moist silver oxide.



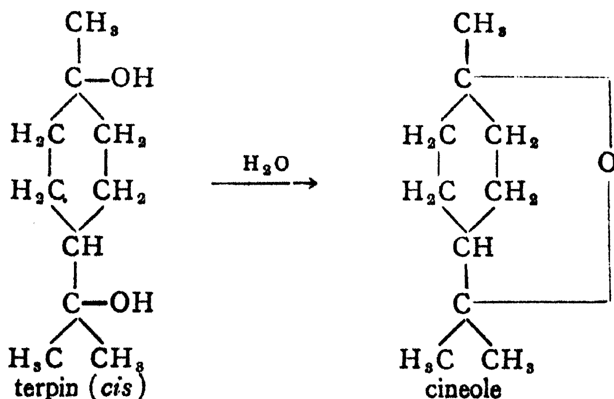
Terpin (*cis*) on dehydration gives different products depending on the dehydrating agents used :

(*a*) α-terpineol (with H_3PO_4)
(*b*) cineole (with oxalic acid)
(*c*) dipentene (with $KHSO_4$)
(*d*) terpinene and terpinolene (with H_2SO_4-glacial acetic acid)

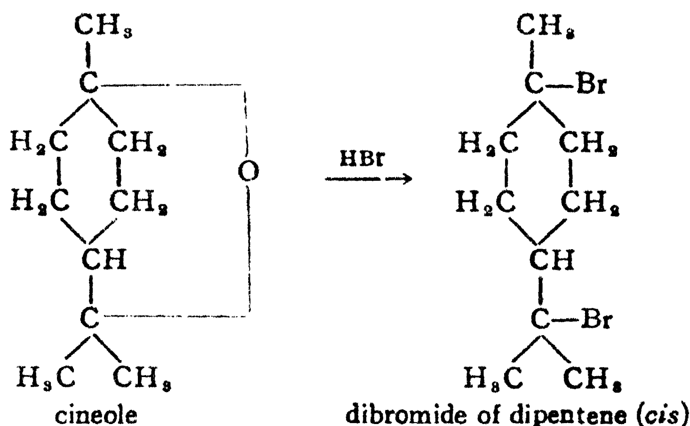
The products (*c*) and (*d*) will be discussed later on. (For dehydration to terpineol, see p. 236).

Cineol has the molecular composition $C_{10}H_{18}$. It is also known as eucalyptole. It is present in many essential oils *e.g.* oil of ecucalytus and oil of worm seed. Its constitution is based on the following evidence :

Cineole gives no positive tests for the presence of hydroxyl or carbonyl groups. The oxygen, therefore, is probably present as an ether (*-O-*) linking. Its formation from terpin (*cis*) points to the same conclusion. The internal ether linking is formed by the elimination of the molecule of water from the two hydroxyls in *cis* position.

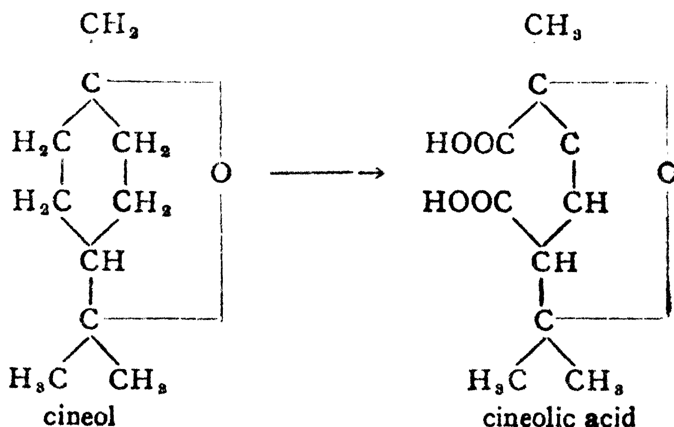


Hydrobromic acid in acetic acid solution converts cineole into *cis* dibromide of dipentene, which is in good agreement with the above structure.



cineole dibromide of dipentene (*cis*)

Cineole readily adds halogens, halogen acids, phenols etc. to form the corresponding oxonium salts. On oxidation with potassium permanganate, cineole, breaks, into cineolic acid.

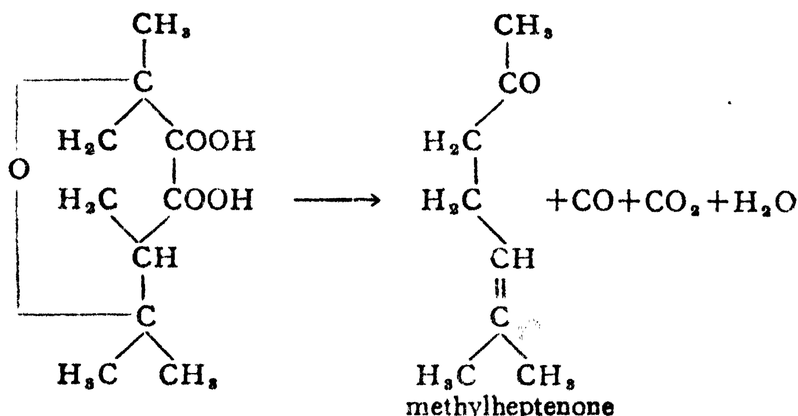


cineol cineolic acid

The results indicate the greater stability of the penta methylene ring as compared with the cyclo-hexane ring.

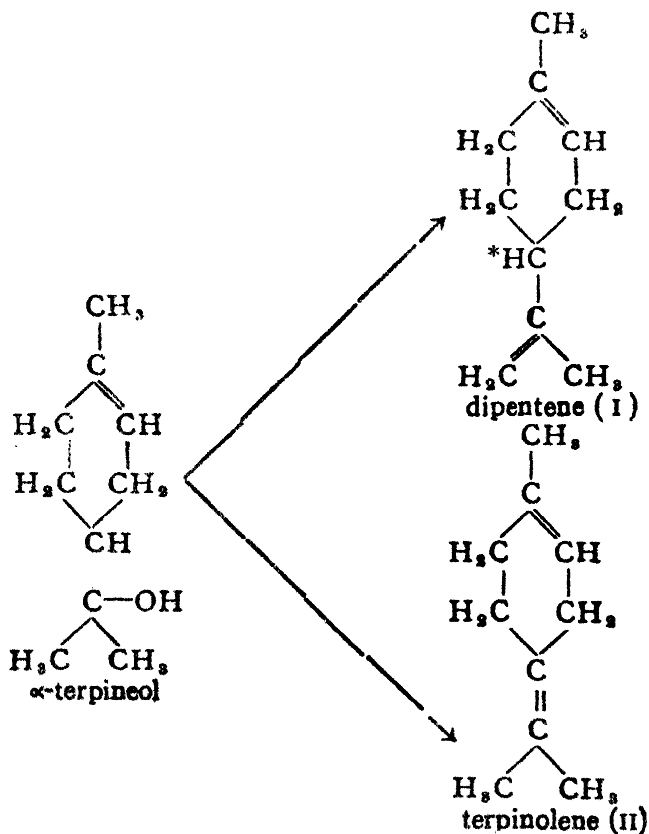
Cineolic acid on boiling with acetic anhydride, gives cineolic anhydride which on dry distillation, forms metheyl heptenone.

This decomposition of cineolic acid into methyl heptenone establishes a link between the mono-cyclic terpenes and the olefinic terpenes which are very closely related to the aliphatic ketone, methyl heptenone.



methylheptenone

(iii) DEHYDRATION OF α-TERPINEOL :—The dehydration leads to the formation of p-menthadienes *e.g.* dipentene, terpenolene and terpinenes. α-Terpineol is a tertiary alcohol and hence readily suffers dehydration. This dehydration may take place in two different ways :-



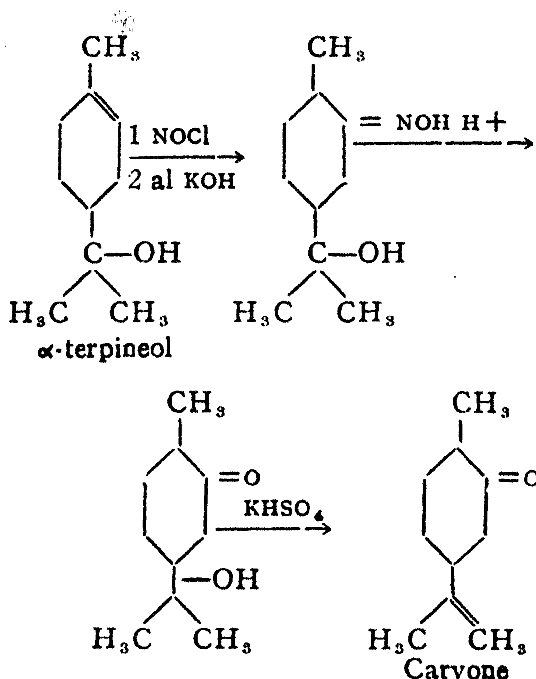
α-terpineol

dipentene (I)

terpinolene (II)

The products formed are both *menthadienes*. The nature of the product formed, depends on the dehydrating agent used. Thus dipentene is formed when α-terpineol is heated with potassium bisulphate, while dehydration by means of alcoholic sulphuric acid gives terpinolene. Baeyer recomends 30% oxalic acid as the best reagent for converting terpineol into terpinolene.

(*iv*) CONVERSION TO CARVONE :—α-terpineol has been converted into carvone—a naturally occuring ketone the steps involved are :—



This is very significant as the inter-relationship between two natural terpenes is thus clearly indicated.

DIPENTENE

Dipentene is the racemic form of *d* and *l* limonenes ; *d*-limonene is the chief constituent of the oil of orange rind, while *l*-limonene is present in oil of pine needles. Dipentene itself occurs in large quantities and oil of turpentine and is formed on dry distillation of rubber and on dehydration of terpin and of α-terpineol.

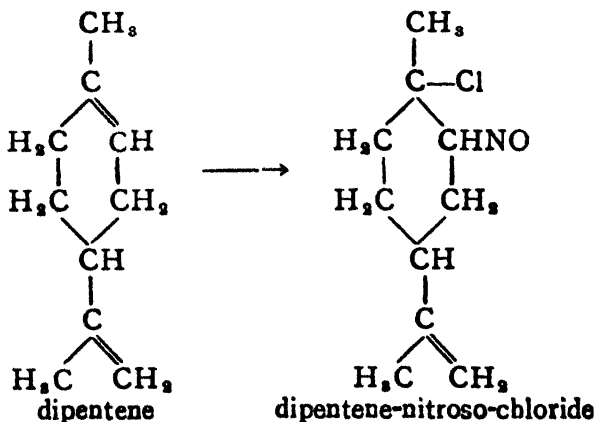
Constitution : Dipentene has the molecular formula $C_{10}H_{16}$; it reacts with bromine to form a terabromide $C_{10}H_{16}Br_4$. It also

reacts with NOCl to form a dinitroso-chloride derivative which is not blue; this rules out the possibility of a double bond in 4-8 positions *i.e.* a semi-cyclic double bond (see p. 224). Thus it contains two double bonds; and as the molar composition is $C_{10}H_{16}$, there must be a ring system in the molecule. On reduction with H_2 and Ni at 180° dipentene is converted into *p*-menthane *i. e.* hexahydro-*p*-cymene. Hence dipentene contains a six-membered ring. Further elucidation of the structure is based on: (*a*) its relation to α-terpineol (*b*) its conversion into 2-hydroxy-*p*-toluic acid and (*c*) its relation to carvone (*d*) its normal molar refraction.

(*a*) Dipentene can be obtained from α-terpineol by dehydration; hence it must be represented by either formula I or II (see p. 237). The choice between the two formulæ rests on the following evidence: Dipentene is a racemic compound capable of being resolved into active *d* and *l* limonenes. It must therefore contain an asymmetric carbon atom. Formula I is asymmetric, carbon atom marked with asterisk is asymetric while II is symmetrical.

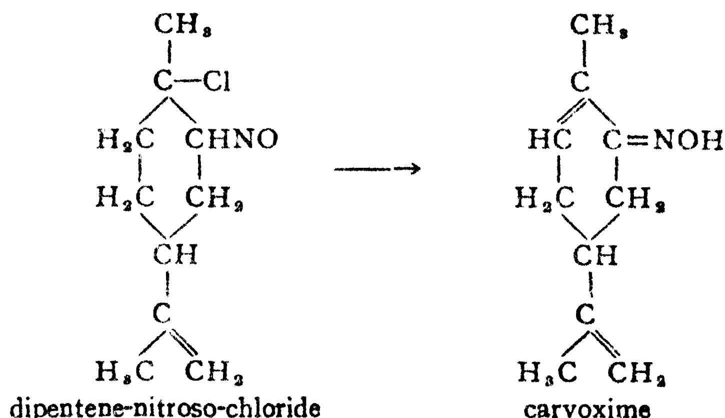
(*b*) Dipentene can be converted through a series of reactions into 2-hydroxy-*p*-toluic acid. These reactions can only be accounted for by assuming that dipentene possesses the formula I; schematically, the reactions involved are:—

Nitrosyl chloride reacts with dipentene to form the corresponding nitroso-chloride:



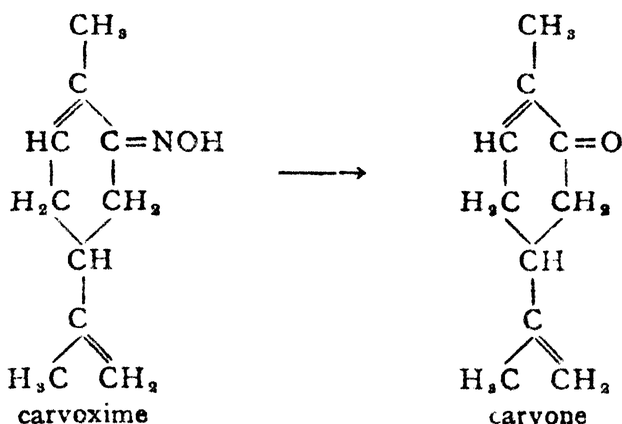
dipentene dipentene-nitroso-chloride

On boiling the nitroso-chloride derivative whit alcholic potash, a molecule of hydrochloric acid is lost and carvoxime is formed.



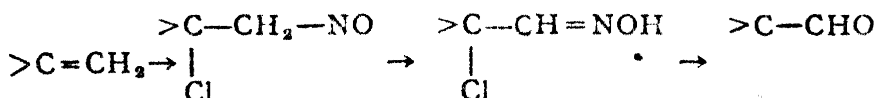
dipentene-nitroso-chloride carvoxime

Hydrolysis of carvoxime with aqueous oxalic acid or with acetic acid and HCl, gives the carvone, which is an un-saturated ketone.

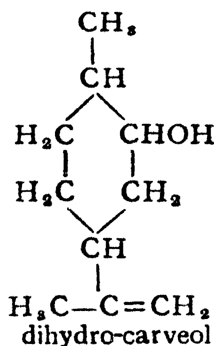


carvoxime carvone

If the double bond in the side chain were attacked by NOCl, the final product of this series of reactions would have been an un-saturated aldehyde:



By reduction with sodium and alcohol, the carbonyl group is changed into *CHOH* group and the double bond in the nucleus is saturated (probably because it is conjugated with $C=O$ group) to give dihydro-carveol. The double bond in the side chain, which is isolated is not attacked by the reagent.



dihydro-carveol

Graded oxidation of dihydro-carveol gives successively tri-hydroxy-hexahydro-cymene, a ketonic alcohol and a hydroxy acid which on dehydrogenation with bromine at 190° is converted into 2-hydroxy *p*-toluic acid.

```
     CH3                       CH3                        CH3
      |                         |                          |
      CH                        CH                         CH
     /  \                      /  \                       /  \
  H2C    CHOH              H2C    CHOH                H2C    CHOH
   |      |       O2        |      |         O2        |      |
  H2C    CH2   -------->  H2C    CH2     -------->   H2C    CH2
     \  /       KMnO4       \  /           CrO3         \  /
      CH                     CH                          CH
      |                      |                           |
      C                      C—OH                        C=O
     / \\                   /  \                        /
  H3C   CH2              H3C   CH2OH                 H3C
 dihydro-carveol       tri-hydroxy-hexa           ketonic alcohol
                        hydro-cymene
                                                      ↓ NaOBr
      CH3                                             CH3
       |                                               |
       C                                               C
     /  \\                                           //  \
   HC    C—OH                  Br2               H2C    CHOH
   |     ||                 <--------             |      |
   HC    CH                    190°              H2C    CH2
     \\  /                                          \  /
       C                                             CH
       |                                             |
     COOH                                          COOH
 2-hydroxy p-toluic acid
```

The formation of the ketonic alcohol, indicates the presence of a double bond in the isopropyl chain, which has escaped the attacks of nitrosyl chloride and of hydrogen (reduction).

The above series of reactions are thus in good agreement with formula I, which contains an asymmetric carbon atom and a double bond in the isopropyl side chain.

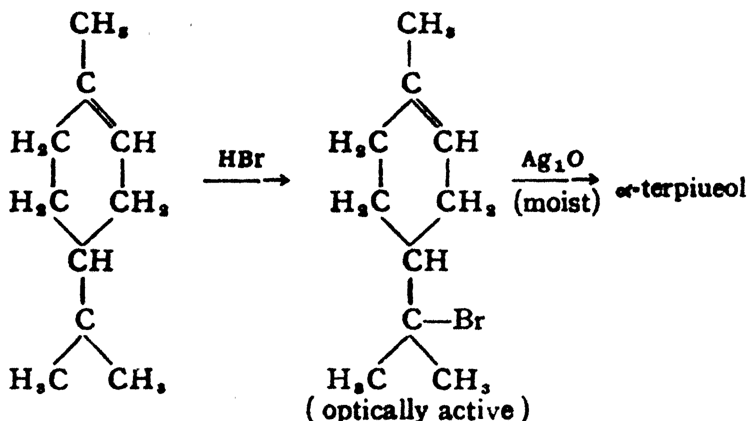
(c) The other formula II which contains a semicyclic linkage is ruled out as the molecular refraction is normal. The presence of a semicyclic system of double bonds is known to lead to an exaltation of the molar refraction. The absence of a semicylic linkage, is also confirmed by the nonformation of a blue nitrosochloride :

The above structure for dipentene is also confirmed by the results of graded oxidation of the molecule, which also suggest a close relationship to α-terpineol.

Dipentene → methylketone → terpenylic acid → terebic acid.

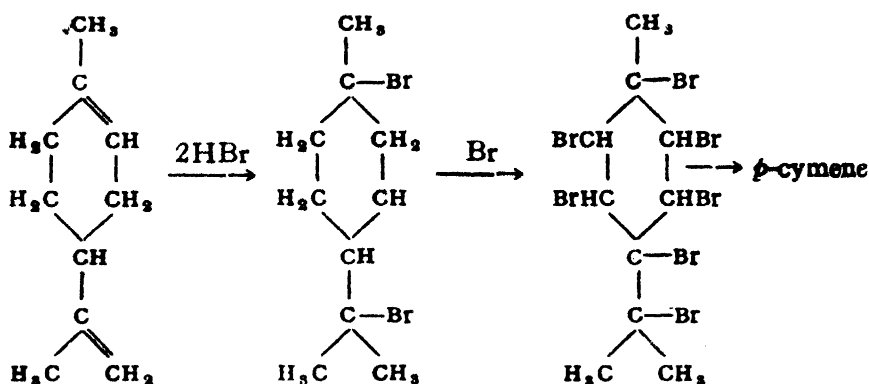
(*cf.*) The oxidative degradation of α-terpineol.

Dipentene is converted into α-terpineol according to the following scheme :



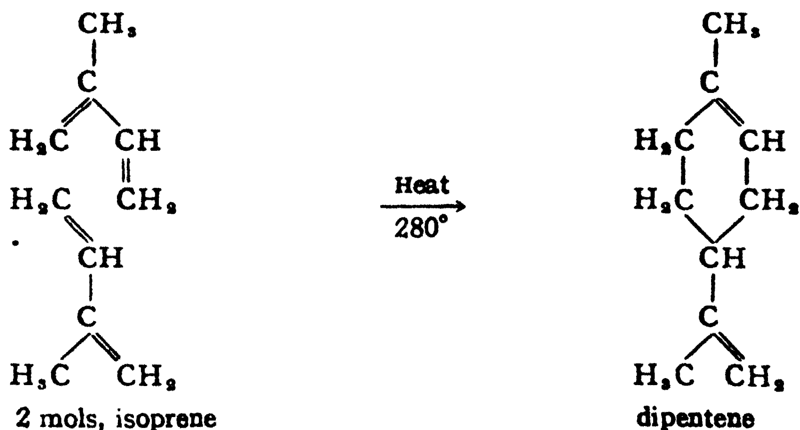
Also, on shaking with 5% H_2SO_4, dipentene is converted into α-terpineol.

Relation to p-cymene : Dipentene with *HBr* gives a dihydrobromide which is identical with 1-8 dibromomenthane ; the latter on bromination and reduction gives *p*-cymene.

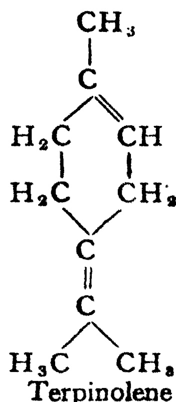


Catalytic hydrogenation in presence of Ni at 180°C, converts dipentene into *p*-menthane dipentene; suffers disproportionation and is coverted into a mixture of *p*-menthane and *p*-cymene, on boiling with Cu-Ni-formate.

SYNTHESIS OF DIPENTENE :—In addition to the synthesis of dipentene from α-terpineol, dipentene can be obtained from isoprene by a process of polymerisation (1-4 addition) :—



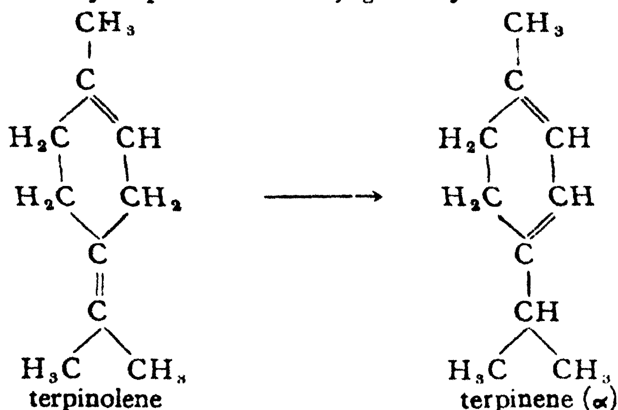
TERPINOLENES AND TERPINENES :—Terpinolene is isomeric with dipentene and its structure is represented by the alternative formula :—



Terpinolene

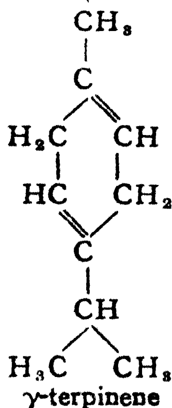
On treatment with acids, it undergoes an isomeric change and forms a mixture of three isomeric menthadienes, α, β, γ-terpinenes (Wallach). The change involves the shifting of the double bond.

Terpinolene contains an isolated system of double bonds which shows a tendency to pass into a conjugated system.

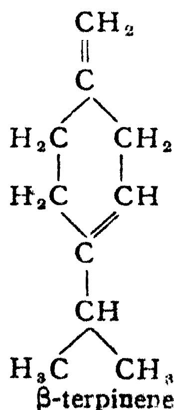


terpinolene — terpinene (α)

Small quantities of the other structural isomers are also formed. They are called β and γ terpinenes :—



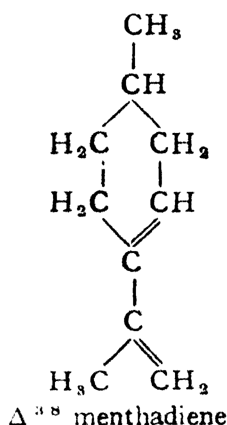
γ-terpinene



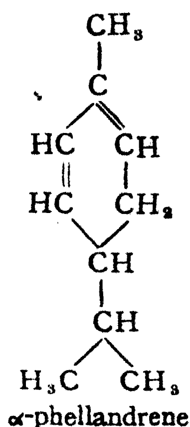
β-terpinene

α-Terpinene and γ-terpinene are always found together in oils of cardamom, coriander and Manila elemi.

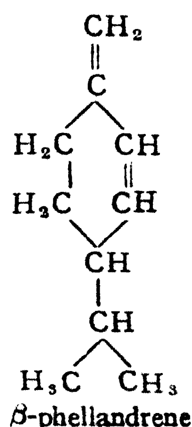
Some other representative menthadienes are:—



$\Delta^{3,8}$ menthadiene



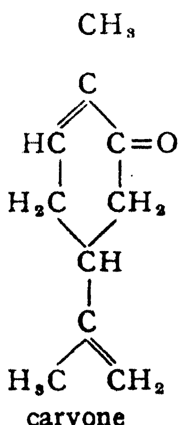
α-phellandrene



β-phellandrene

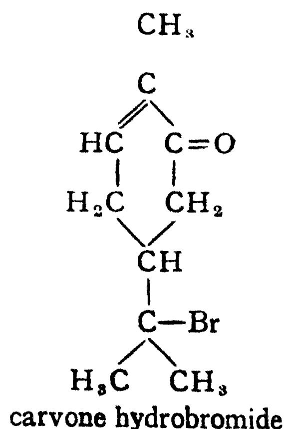
α and β phellandrenes are present together *in many essential* oils *e. g.* ginger grass oil, oil of bitter fennel and oil of eucalyptus. The constitution of α-phellandrene follows *from its relation to* Δ_1 menthene, into which it can be converted by suitable reduction. It can also be synthesised from carvone in the following way :—

Carvone with hydrobromic acid forms a hydrobromide.



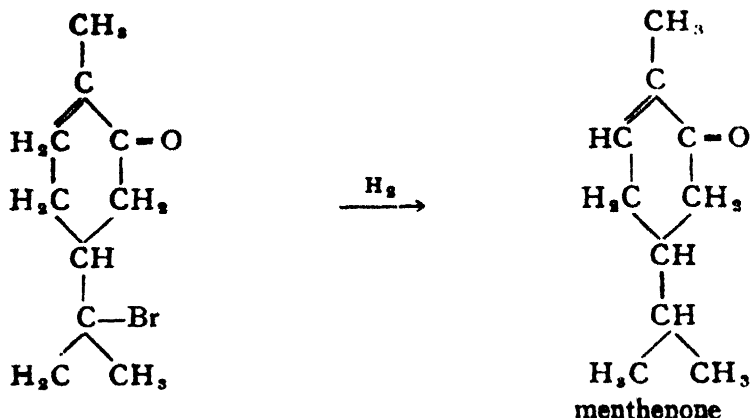
carvone





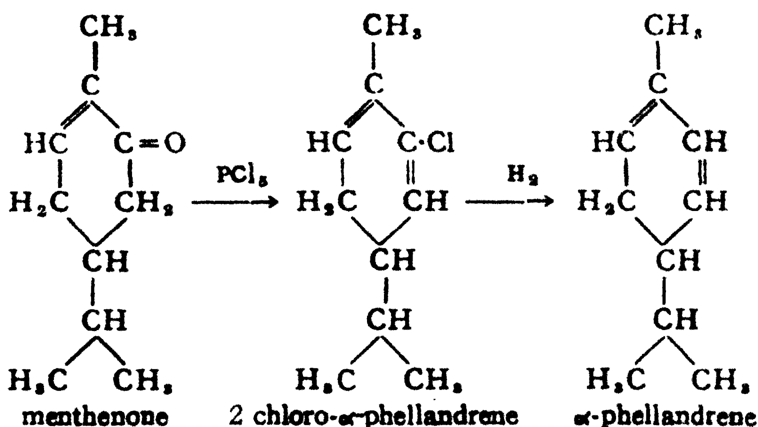
carvone hydrobromide

The hydrobromide on reduction with zinc dust and methanol is converted into menthenone:



menthenone

Menthenone on treatment with phosphorus pentachloride and subsequent reduction with zinc and methanol gives ∝-phellandrene.



Pulegone is a ketone related to *p*-menthane. It is found in the oil of pennyroyal.

Constitution : The molecular composition of pulegone is $C_{10}H_{16}O$. It gives the following reactions :

(*a*) It reacts with bromine to form a dibromide $C_{10}H_{16}OBr_2$. Hence it contains a double bond.

(*b*) It reacts with hydroxylamine under neutral conditions to give an oxime. This indicates a CO group in the molecule.

(*c*) On reduction, it is first changed into menthone and finally in to menthol. These results indicate that it has the same carbon

skeleton as menthone or menthol. The position of the keto group is also thus established :—

$$H_3C-C\begin{cases}C—C=O\\C—C\end{cases}C-C\begin{cases}CH_3\\CH_3\end{cases}$$

But pulegone is an unsaturated ketone, with a double bond. The position of the double bond is established by the reactions of the compound with (*a*) hydroxylamine and (*b*) with water under pressure or with anhydrous formic acid.

Pulegone with hydroxylomine gives an oxime, or a hydroxylamine derivative, depending on experimental conditions.

$$C_{10}H_{16}O + H_2NOH \xrightarrow{\text{Neutral}} C_{10}H_{16}NOH$$

oxime of pulegone

$$C_{10}H_{16}O + H_2NOH \xrightarrow[\text{(alkaline)}]{NaOCH_3} C_{10}H_{17}O{\cdot}NHOH$$

hydroxylamine derivative of pulegone

i. e. a molecule of hydroxylamine is added on to the molecule of pulegone at the double bond uuder weakly alkaline conditions. Such a behaviour is typical of an ∝-β-unsaturated ketone, for, mesityl oxide gives with hydroxylamine, both an oxime and the di-acetone hydroxylamine derivative, depending on the conditions.

$$(CH_3)_2C=CH-C(=N-OH)-CH_3$$

oxime

$$\frac{H_3C}{H_3C}\Big>C=CH-CO-CH_3$$

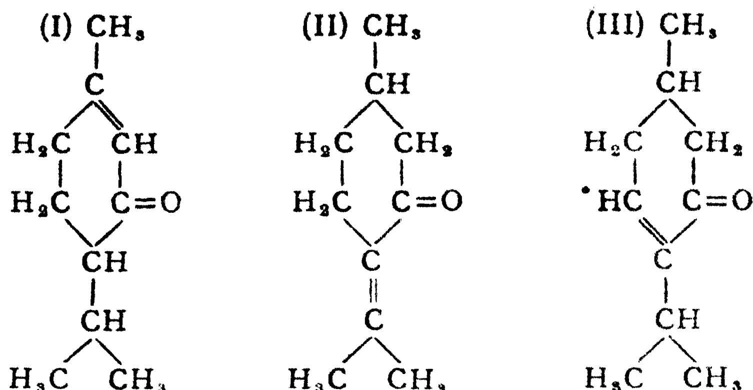
$\xrightarrow{NH_2OH}$ oxime (above)

$\xrightarrow{NH_2OH,\ NaOCH_3}$

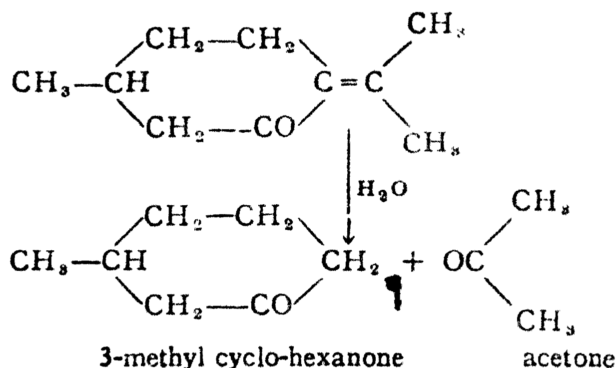
$$(CH_3)_2C(NHOH)-CH_2-CO{\cdot}CH_3$$

di-acetone hydroxlamine derivative

Pulegone, therefore, must be an ∝-β-unsaturated ketone. The position of the keto group is 3 and hence, pluegone may have one of the following structural formulas :—

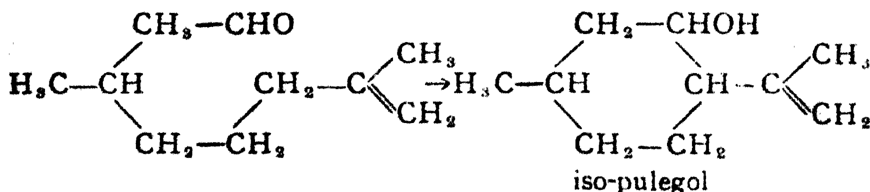


The behaviour of pulegone, on heating with water under pressure, decides between these three possible formulas. Wallach found that when pulegone is heated with water under pressure, acetone and 3-methyl cyclo-hexanone formed. Only formula II can account for such decomposition products :—



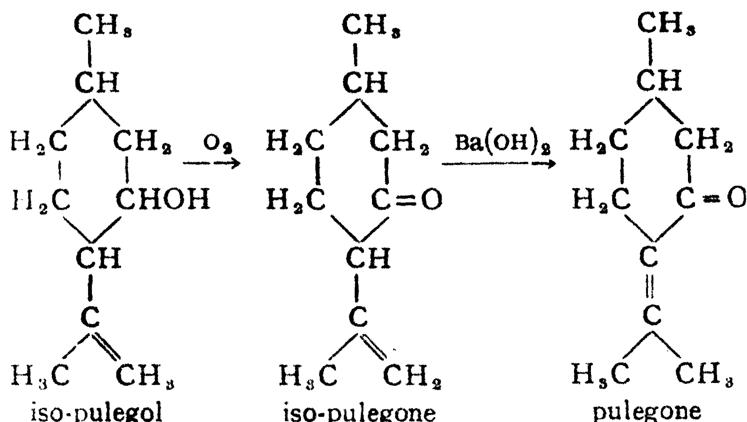
3-methyl cyclo-hexanone acetone

A *Synthesis* of pulegone from citronellal has been achieved by Tiemann and Schmidt. When citronellal is boiled with acetic anhydride, cyclisation takes place with the of formation of isopulegol :—



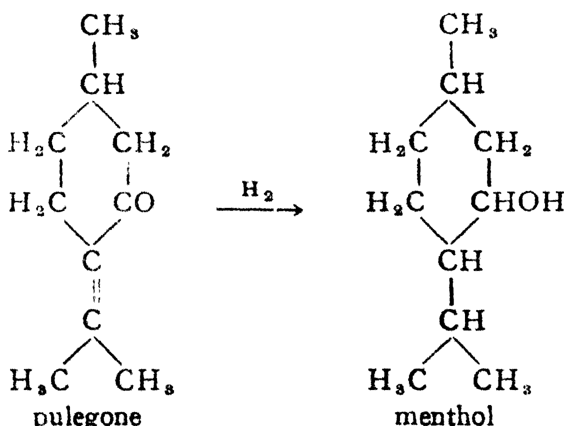
iso-pulegol

Iso-pulegol is then oxidised by chromic acid to isopulegone and the latter, on boiling with barium hydroxide, is changed into pulegone :—



iso-pulegol iso-pulegone pulegone

Finally, pulegone on reduction forms menthol, which thus confirms its structure :—



pulegone menthol

CARVONE

Carvone exists as *d*, *l*, and *dl* modifications in many essential oils. Oil of carraway contains a large quantity of *d*-carvone. *l*-Carvone is found in oil of kuromoji. The molecular composition is $C_{10}H_{14}O$. It contains two double bonds and one keto group as is indicated by the formation of a tetra-bromide with bromine and an oxime with hydroxylamine. Its structural formula is based on the following evidence :—

(*a*) On heating with sulphuric acid and phosphoric acid, it isomerises into carvacrol, *i.e.* *β*-hydroxy-*p*-cymene. This reveals the skeleton with the keto group in position two ; The keto group of carvone is enolised in carvacrol :

```
              O
              ‖
              C—C          CH₃
             /    \       /
   H₃C—C<          >C—C<
             \    /       \
              C—C          CH₃
```

(*b*) Carvone contains two double bonds; with mild reducing agents like zinc and alcoholic potassium hydroxide, carvone takes up two atoms of hydrogen to form dihydro-carvone which still contains one double bond. On oxidation with potassium permanganate, dihydro-carvone is changed into 4-acetyl-1-methylcyclo-hexanone.

```
              O
              ‖
              C——CH₂
             /       \
   H₃C—CH<            >CH—COCH₃
             \       /
              CH₂—CH₂
```

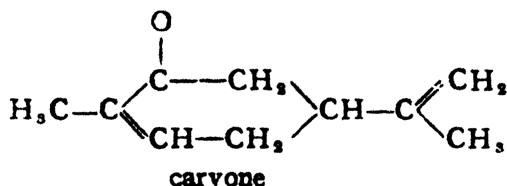
4-acetyl-1-methyl-cyclo-hexanone

The structure of this ketone is established by its conversion into *m*-hydroxy-*p*-toluic acid. These results show that the double bond in dihydro-carvone is located in the isopropyl sidechain. Hence, one of the two double bonds in the molecule is proved to be in the isopropyl side-chain. The position of the double bond in the nucleus is proved in the following way.

Carvone with hydrobromic acid gives a hydrobromide when the double bond in the side-chain is saturated. Reduction of the hydrobromide forms carvo-tanacetone, isomeric with dihydrocarvone. On oxidation with potassium permanganate, carvotanacetone gives pyruvic acid and isopropyl succinic acid; and as the oxidation takes place at the double bond, it follows that in carvotanacetone, the double bond is situated between the carbon atoms 1 and 6.

```
         O
         ‖                        CH₃    CH₃            CH₂—COOH
         C——H₂C                  /       |              |
        /       \               /        |              |
  H₃C—C<         >CH—CH  ——→   CO—COOH  +  CH—COOH
        \\      /       \        |              |
         CH—CH₂          \       |              |
                          CH₃   CH₃             C₃H₇
```

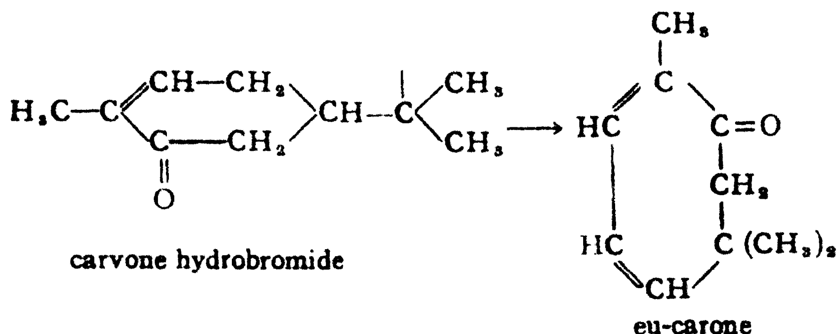
Hence, it follows that the other double bond in carvone is in the nucleus between positions 1 and 6. The structure of carvone is therefore :—



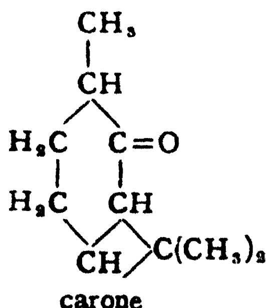
carvone

RELATION TO DIPENTENE :—Carvone is closely related to dipentene. The oxime of carvone is identical with nitroso-limonene. Dipentene can thus be readily converted into carvone. Wallach has also reported a conversion of α-terpineol into carvane.

Carvone undergoes transformation reactions which are of great interest. The hydrobromide of carvone on treatment with alkali loses a molecule of hydrobromic acid but forms eu-carvone which contains a seven-membered ring system.



On the other hand, the hydrobromide of dihydro-carvone under the same conditions, gives carone, a compound with a di-cyclic system.



carone

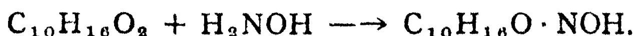
BUCHU CAMPHOR OR DIOSPHENOL

OCCURENCE AND STRUCTURE :—It is present in the oil of bukku leaves. Its structural formula is based on the researches of Semmler and McKenzie.

The molar composition of Buchu camphor is $C_{10}H_{16}O_2$.

(*a*) It readily forms a mono-acetate and a mono-benzoate, which indicates the presence of a hydroxyl group.

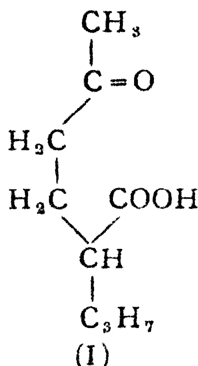
(*b*) With hydroxylamine, an oxime is formed:



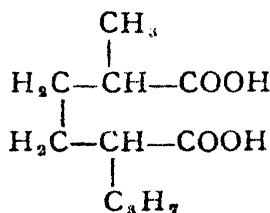
$$C_{10}H_{16}O_2 + H_2NOH \longrightarrow C_{10}H_{16}O \cdot NOH.$$

Hence, Buchu camphor is a ketonic alcohol.

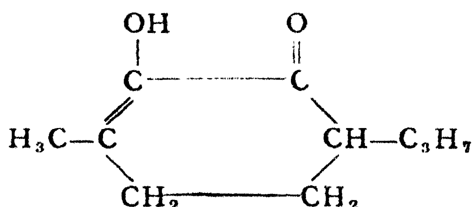
Nature of the carbon framework:—On oxidation with ozone, Buchu camphor is converted into α-isopropyl -γ-acetyl-*n*-butyric acid (I).



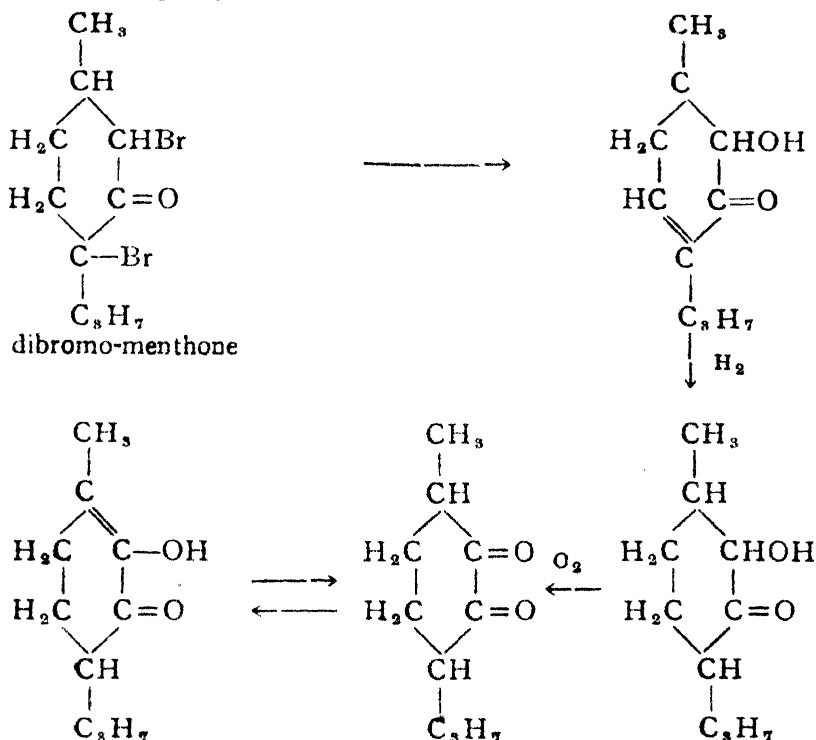
Reduction of the camphor gives a glycol, which on oxidation, is changed into α-isopropyl-α-methyl adipic acid :—



These results indicate that the camphor molecule must contain (*a*) a six-membered ring system and (*b*) the methyl and isopropyl groups are in *para* positions to each other. Further, it is obvious that the keto and hydroxyl groups must be present on the carbon atoms, which appear as carboxyl groups. But the formation of (I) with a CH_3CO-group shows that the double bond is adjacent to the CH_3 group. This leaves position 3 for the keto group. The hydroxyl group, therefore, must be present on C_2. Hence the complete structure is :—



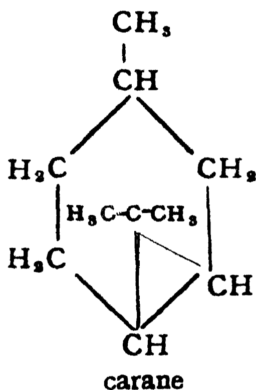
SYNTHETICALLY, it may be obtained from dibromo-menthone in the following way :—



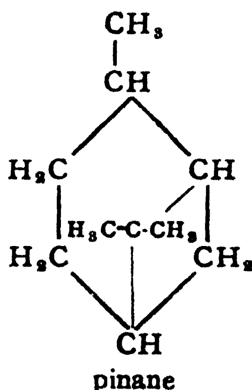
DICYCLIC TERPENES AND CAMPHORS

The terpenes belonging to these systems have the same molecular composition $C_{10}H_{16}$ as those of monocyclic system and are thus isomeric with them. They are readily converted into *p*.cymene or *p*-menthane by the reagents used in connection with the terpenes of the mono-cyclic system and hence are also derived from *p*-menthane. However, they add only one molecule of hydrochloric acid or of bromine and therefore contain only one double bond, instead of two as the terpenes of the monocyclic system do. But they contain four hydrogen atoms less than the saturated compound, *p*-menthane

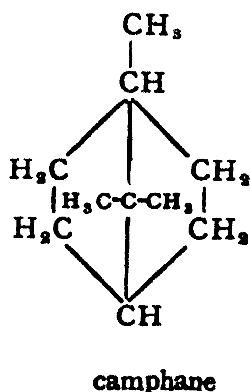
$C_{10}H_{20}$; it therefore follows that there is a second closed ring in the molecule. This can be pictured as follows: the isopropyl chain of the *p*-menthane may be folded in, to form a second bridge ring system in any one of the following ways, wherein the tertiary carbon atom and another from the ring, are involved in the second ring formation.



carane

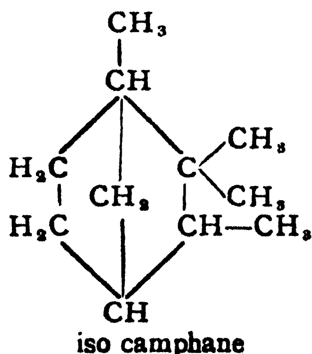


pinane

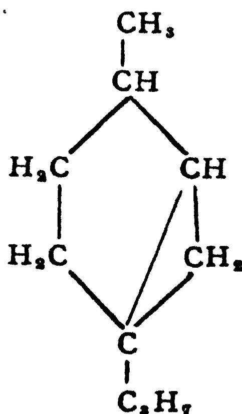


camphane

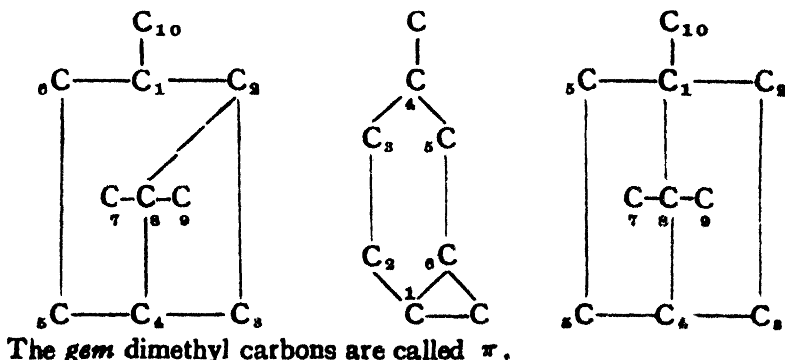
Thus we have the three dicylic systems: carane, pinane and camphane. There is another different camphane system called iso-camphane. Carane contains an additional trimethylene or cycol-propane system, while pinane contains a tetramethylene, or cyclo-butane system and camphane a pentamethylene or cyclopentane system. The smaller endo-cyclic systems are stable towards the usual addition reactions, being probably stabilised by the presence of the *gem* dimethyl group. However, under the action of heat or hydrating agents they are opened up readily to form derivatives of monocyclic systems. The terpenes which represent the corresponding unsaturated compounds with one double bond are termed carene, binene and camphene respectively. There is another family of di-cyclic terpenes, which is derived from thujane (sabinane). They are called thujanes.



iso camphane



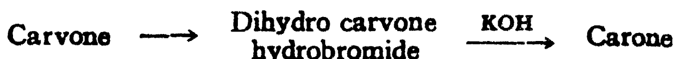
The numbering of the carbon atoms in the carane, pinane and camphane series is different from that adopted in the menthane series :—



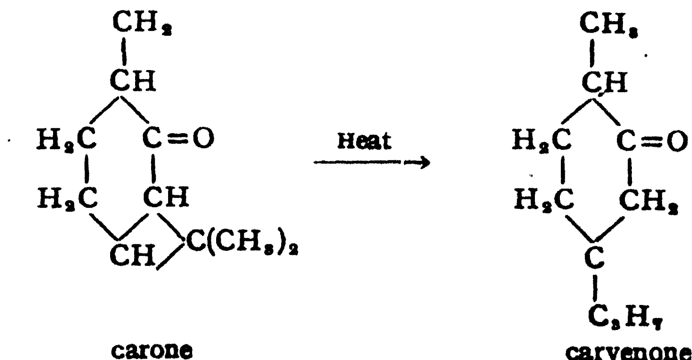
The *gem* dimethyl carbons are called π.

Carane Group

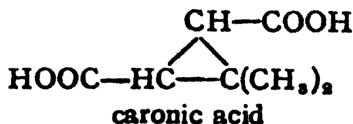
The most important member of this series is *carone*. It is a ketone. It is synthesised from carvone.



On heating, carone is converted into carvenone, thereby cleaving the trimethylene ring.



The presence of the cyclo-propane or trimethylene ring is proved by the oxidation of carone to caronic acid.



caronic acid

The conversion by Baeyer, of carone into *dl*-sylvestrene, a derivative of *m*-menthene, is of some interest. The essential steps in the conversion are :—

With hydroxylamine, carone, is changed into its oxime.

```
      CH3                                      CH3
      |                                        |
      CH                                       CH
     /  \                                     /  \
  H2C    C=O                               H2C    C=NOH
   |     |          H2NOH                   |     |
  H2C    CH       -------->                H2C    CH
     \  /  \                                  \  /  \
      CH ---C(CH3)2                            CH ---C(CH3)2
```

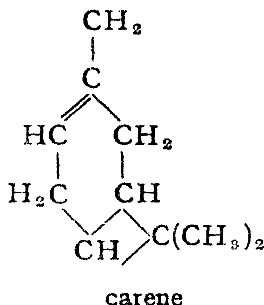
On reduction, the corresponding amine is obtained, which on warming with (alcoholic) acid, is changed into vestryl amine.

```
     CH3                  CH3                     CH3
     |                    |                       |
     CH                   CH                      CH
    /  \                 /  \                    /  \
 H2C    C=NOH         H2C    CH-NH2   HCl     H2C    CHNH2
  |     |       H2     |     |       ---->     |     |       CH2
 H2C    CH     ---->  H2C    CH               H2C    CH--C<
    \  /  \              \  /  \                 \  /        CH3
     CH ---C(CH3)2        CH ---C(CH3)2           CH2
 carone.oxime          caryl amine             vestryl amine
```

The cyclo propane ring is opened up and at the same time, the isopropylene group appears in the *meta* position to the methyl group, giving vestryl amine. The hydrochloride of vestryl amine, on dry distillation, forms carvestrene—the racemic form of sylvestrene.

```
      CH3                                    CH3
      |                                      |
      CH                                     C
     /  \                                   // \
  H2C    CH—NH2HCl                       H2C    CH
   |     |        CH2                     |     |        CH2
  H2C    CH—C<          ---------->      H2C    CH—C<
     \  /        CH3                        \  /        CH3
      CH2                                    CH2
                                        dl-sylvestrene
```

CARENES :—The terpenes derived from carone are found in small quantities in many essential oils. The carene present in the oil of Indian turpentine is Δ_3 carene, and is the most common.



carene

According to Simonsen, the carenes are very susceptible to the action of mineral acids. During their isolation and purification, their cyclo-propane ring opens up with the formation of a terpene belonging to a *p*-menthane or *m*-menthane series; Δ_3 carene may thus be converted into dipentene or sylvestrene.

```
                      CH3
                      |
                      C
                    //  \
                  HC     CH2
                  |      |
                 H2C     CH
                    \   / \
                     CH    >C(CH3)2
                       \  /

                   Δ3 carene
                  /         |
                 ↙          ↓

  CH3          CH3          CH3                          CH3
  |            |            |                            |
  C            C—Cl         C—Cl                         C
 // \         /  \         /  \                         // \
HC   CH2 KOH H2C  CH2    H2C  CH2     Cl      ——→      HC   CH2
|    |   ←— |     |      |    |       |   /CH3         |    |       //CH2
H2C  CH2    H2C  CH2     H2C  CH—C<                    H2C  CH—C<
  \  /        \  /         \  /         \CH3             \  /       \CH3
   CH          CH           CH2                           CH2
   |           |
   C           C—Cl                                    sylvestrene
  / \\        /  \
H3C  CH2    H3C  CH3
dipentene
```

dipentene

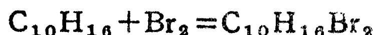
sylvestrene

PINANE GROUP

Pinene is the representative of the terpenes belonging to this group. It is the most abundant of all terpenes. It is an oil b.p. 155°. It is the chief constituent of the oil of turpentine, from which it is separated by fractional distillation. Closely associated with it in nature is the isomer β-pinene or norpinene which probably differs from it in the position of the double bond. Pinene is optically active and exists in *d*, *l* and *dl* forms.

The chemistry of pinene in particular, and of the dicyclic terpenes in general, is much more difficult, as these compounds undergo remarkable isomeric changes involving the fission of one of the two rings, followed by the formation of a briged ring structure of a new type and of greater stability. Pinene with hydrochloric acid is readily changed into bornyl chloride, a compound belonging to the camphane system. On oxidation, pinene can be converted into terpenylic acid and terebic acid, thus suggesting a close relationship to terpineol and dipentene. It can also be oxidised to pinonic acid, pinic acid, and norpinic acid. Thus at one time, several formulas were developed for pinene. The present formula which accounts for most of the facts about pinene is based on the extensive investigations of many chemists such as Wallach, Sobrere, Wagner and Baeyer.

CONSTITUTION OF α PINENE :—The molecular composition of α-pinene is $C_{10}H_{16}$. It contains only one double dond as is indicated by the formation of a nitroso-chloride $(C_{10}H_{16}NOCl)_2$. This reaction is employed for the isolation and identification of α-pinene. [When heated with aniline, the alcoholic solution of the nitroso-chloride gives pure pinene. Sodium acetate in acetic acid solution, may also be used instead of aniline] With bromine or chlorine also, it forms a crystalline *di*-derivative :



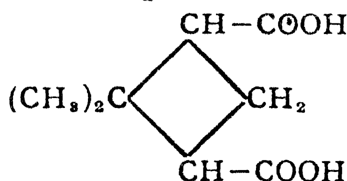
$$C_{10}H_{16}+Br_2=C_{10}H_{16}Br_2$$

With HCl gas at—60°, pinene is converted into pinene hydrochloride, which isomerises to bornylchloride by warming it up to—10°. The latter is a crystalline mass melting at 131-132°. It possesses a camphor-like smell, hence called *artificial camphor.* The change of pinene hydrochloride—a pinane derivative, into bornyl chloride—a camphane derivative is known as Wagner-Meerwein Transformation. When pinene is treated with HCl gas at ordinary temperature, a mixture of chlorides is formed which contains fenchyl chloride isomeric with bornyl chloride.

But the saturated open-chain compound with C_{10} should have the composition $C_{10}H_{22}$; pinene is $C_{10}H_{16}$ *i.e.* it contains six H atoms less ; the additional reactions given above, indicate the presence of only one double bond. Hence there must be *two* ring systems in the molecule.

The nature of these rings is revealed hy the studies in oxidative degradation of pinene.

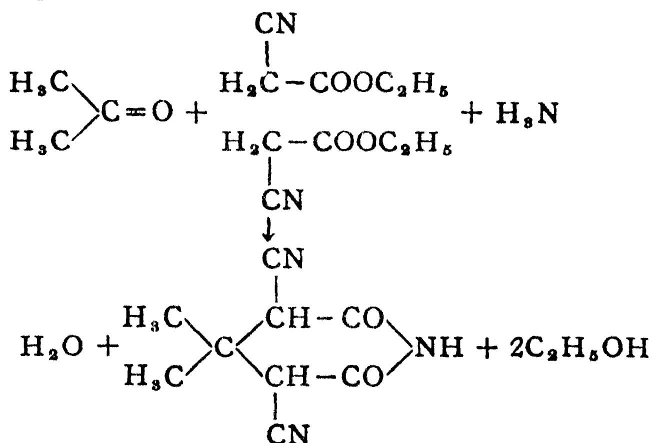
Presence of a cyclo-butane system :—The molecule of pinene is stepwise degraded to pinonic acid, pinic acid and norpinic acid, using different agents under suitable conditions. The last is a derivative of cyclo-butane and has been assigned the structure :—



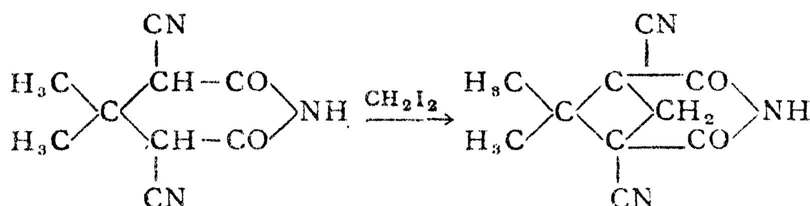
N.B.—Norpinic acid and pinic acid which contain a cyclobutane ring with 1-1-dimethyl groups and side-chains present in position 2 and 4 belong to *piceane* system.

Norpinic acid has heen synthesised by Kerr, by a method which establishes its structure. The essential steps in its synthesis (Guareschis imide synthesis) are :—

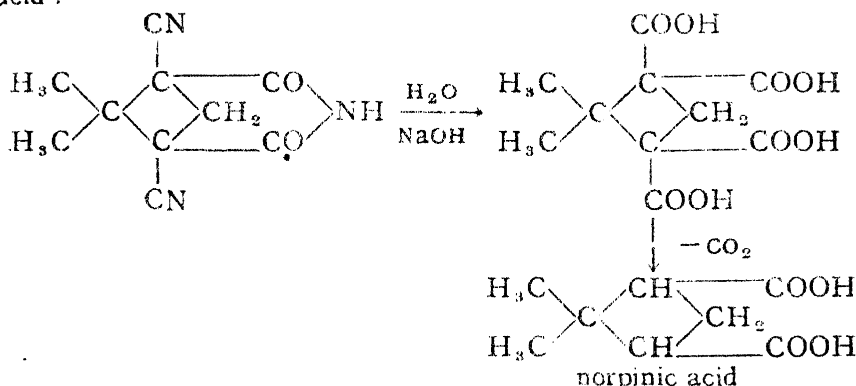
(a) Acetone is condensed with cyano-acetic ester in presence of ammonia to give a cyclic-imide :



(*b*) The imide is treated with methylene iodide (CH_2I_2). in presence of sodium ethoxide when a cyclo-butane ring is closed up ;

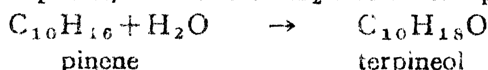


(c) Hydrolysis and subsequent decarboxylation gives norpinic acid :—



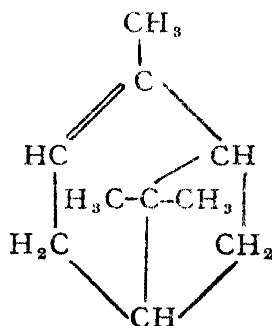
Pinene, therefore, must contain the *cyclo butane* system. The nature of the other ring and the final structure for ∝-pinene is then deducted as follows :

∝-Pinene on boiling with—alcoholic H_2SO_4, forms ∝ terpineol. This established (a) the position of the double bond and (b) the presence of a six-membered ring in the pinene molecule. Further, in the formation of ∝-terpineol, one mole of H_2O is taken up



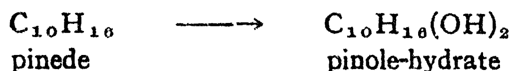
$$C_{10}H_{16} + H_2O \rightarrow C_{10}H_{18}O$$
pinene terpineol

and a hydroxyl group (tertiary) appears on C_8 of the terpineol molecule. This indicates that C_8 of the terpineol molecule is involved in the second ring (namely-four-membered) formation. Hence the formula for pinene is :

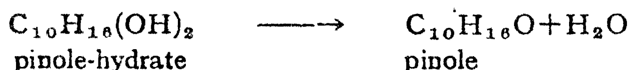


WAGNER S RESEARCHES :—The present structural formula for pinene rests on the researches of Wagner. It is chiefly based on the relation of *pinene to pinole.*

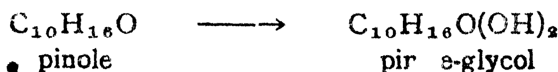
Pinene, in presence of air and moisture or with dilute $KMnO_4$ readily forms pinole-hydrate or *sobrerol* or pinene glycol.



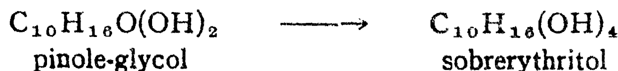
On boiling with acids, pinole-hydrate loses water and is converted into pinole.



This mode of formation suggests that pinole is an internal ether like cineole. Pinole on oxidation with one per cent solution of potassium permanganate gives pinole glycol.

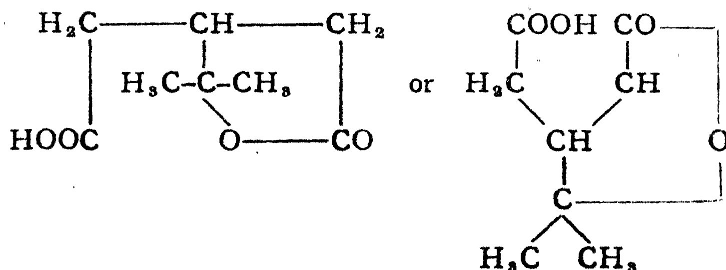


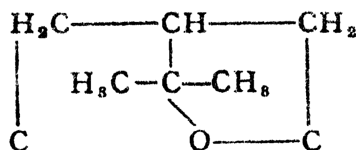
(The double bond in pinole is hydroxylated. Wagner's rule). Pinole-glycol, on further oxidation with $KMnO_4$ at ordinary temperature, yields sobrerythritol which is a tetra-hydric alcohol.



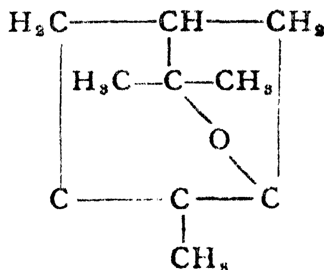
The internal ether linking is broken up here with the addition of the elements of water.

Lastly sobrerythritol (which is *p*-menthane 1, 2, 6, 8 tetrol) is further oxidised to terpenylic acid. Hence, pinole glycol and pinole must contain the same atomic framework as in terpenylic acid, *viz* :

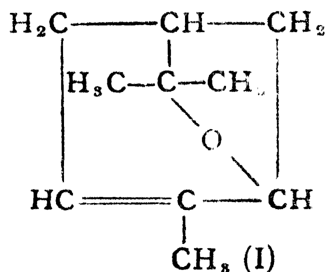


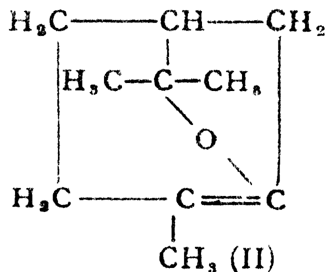


Further, there is a methyl group in *para* position to the isopropyl group as evidenced by the conversion of α-pinene into dipentene or terpineol; the framework could be further evolved as :



Now pinole contains a double bond. That this double bond is adjacent to the methyl group is indicated by (*a*) conversion of pinene into terpineol and (*b*) formation of pinonic acid a methyl ketonic acid,—on oxidation of pinene. Hence, pinole may be either (*I*) or (*II*).

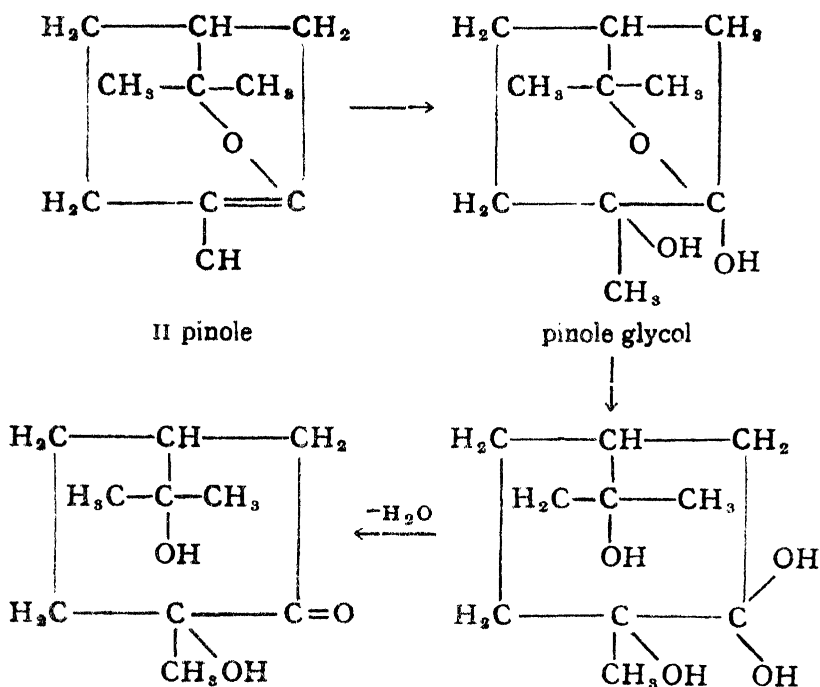




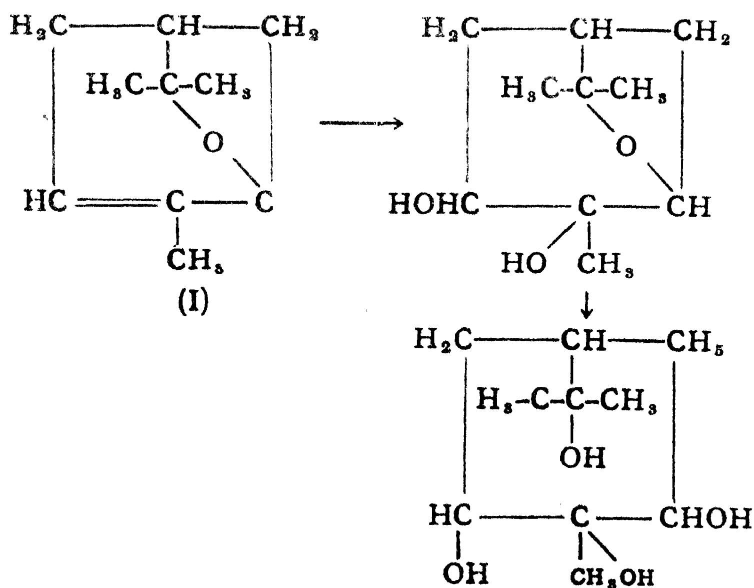
Formula (II) is excluded on the basis of the following evidence :—

Pinole, on oxidation with $KMnO_4$ gives sobrerythritol—a tetra-hydric alcohol (see above). If pinole were II, we would have to represent the changes involved as follows :—

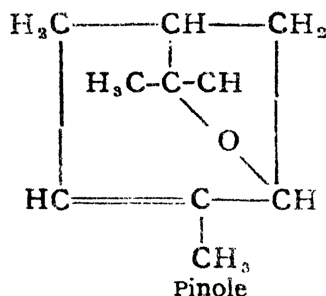
i.e. a dihydric ketonic compound would be formed instead of a tetra-hydric alcohol.



Formula (I), on the other hand, would give under the same conditions, a tetra-hydric alcohol:—



Hence pinole must be represented by (I).

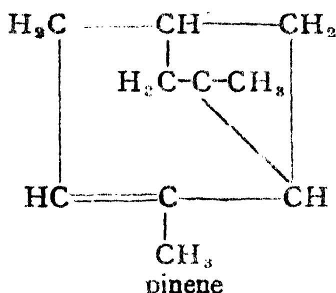


Pinole

The above structure for pinole is confirmed by its synthesis from α-terpineol. The dibromide of α-terpineol, on treatment with sodium ethoxide, is converted into pinole; the different steps in the synthesis are :—

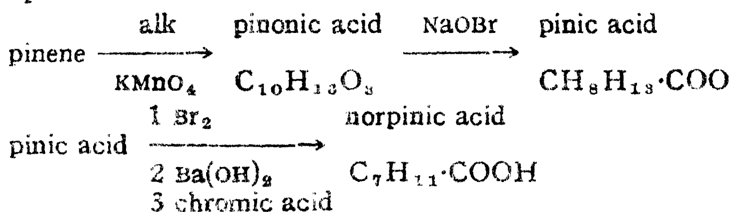
```
     CH3                    CH3                      CH3
     |                      |                        |
     C                      C-Br                     C
    / \\                   / \                     // \
 H2C   CH               H2C   CH-Br              HC    CHBr
  |    |        Br2      |    |      NaOC2H5      |    |
 H2C   CH2    ------>   H2C   CH2   --------->   H2C   CH2
    \ /                    \ /                      \ /
     CH                     CH                       CH
     |                      |                        |
     C-OH                   C-OH                     C-OH
    /  \                   /  \                     /  \
 H3C    CH3             H3C    CH3               H3C    CH3
                         bromide                       |
                         CH3            -HBr           v
                         |         <-----------        CH3
                         C                             |
                       // \                            C
                     HC    CH --                     // \
                     |     |   |                   HC    CHOH
                    H2C    CH2 |      <------      |     |
                       \ /     O                  H2C    CH2
                        CH     |                     \ /
                        |      |                      CH
                        C------                       |
                       / \                            C-OH
                    H3C   CH3                        /  \
                     pinole                       H3C    CH3
```

Pinole is the internal ether derived from pinene; also pinene contains a cyclobutane ring with a gem-dimethyl group. Hence pinene is :—

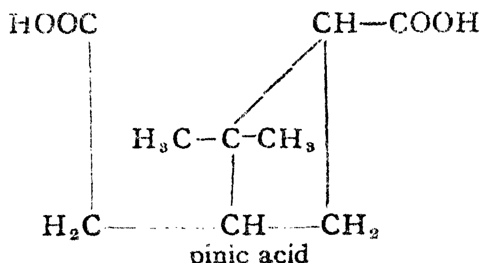


pinene

The structure of pinene can also be deduced from its degradation to norpinic acid.

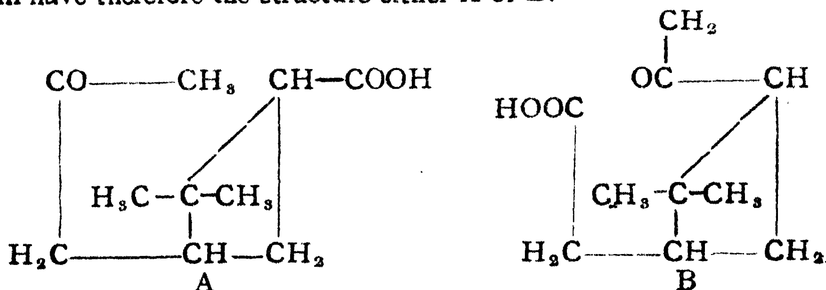


Norpinic acid has the constitution as established by a synthesis (see p. 249); pinic acid which is the higher homologue will have the constitution :—

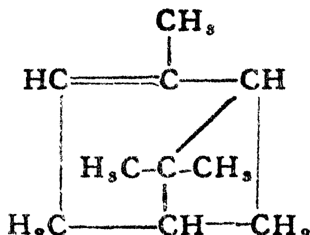


pinic acid

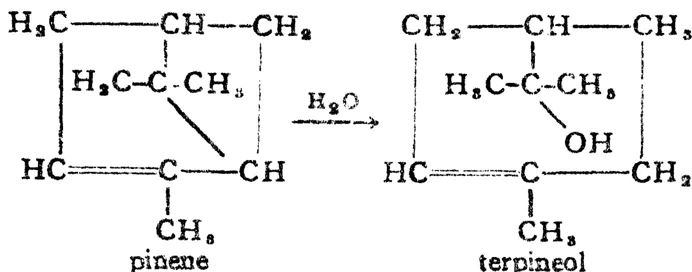
Pinonic acid which is the corresponding methyl ketonic acid will have therefore the structure either A or B.



A is excluded on the ground that pinene on heating with I_2, gives *p*-cymene. *A* would give *m*-cymene. Hence *B* must represent pinonic acid. This acid is obtained from pinene by oxidation which attacks the double bond in the molecule. Hence pinene must be :

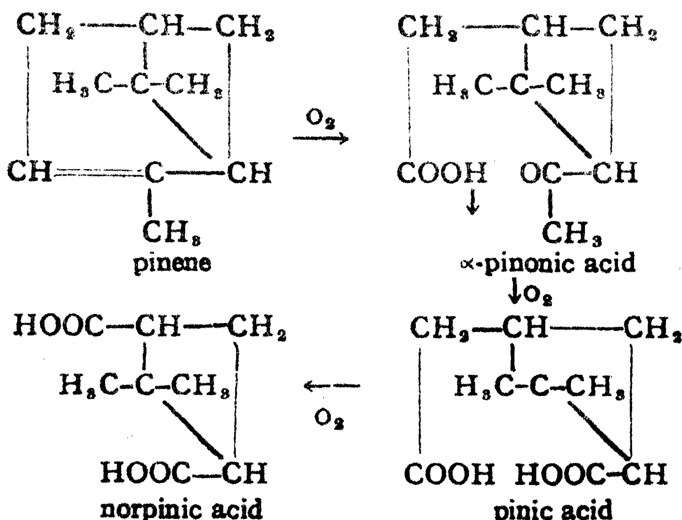


The above formula readily accounts for : (*a*) the presence of a cyclo-butane system, (*b*) the presence of a six membered system, and (*c*) the conversion into α-terpineol :—

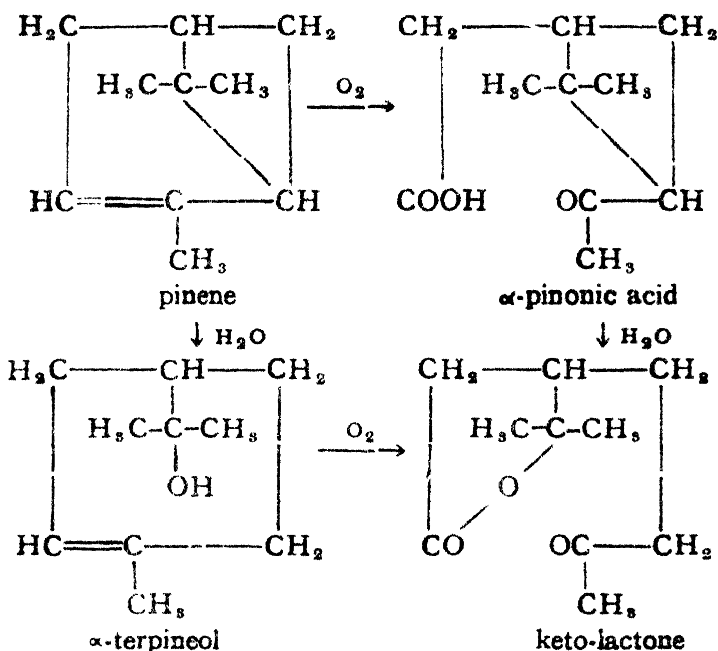


(The fission of the endo-cyclic system takes place)

The graded oxidation of pinene to α-pinonic acid, pinic acid and norpinic acid, is explained as follows :—



The structural formula for ***pinonic acid*** is based on the following observation. α-Pinonic acid, on hydrolysis with 59 per cent sulphuric acid, gives the keto-lactone, homoterpenyl methyl-ketone, identical with that obtained by the oxidation of terpineol. The hydrolysis of pinene into α-terpineol is also known. Hence we have:—

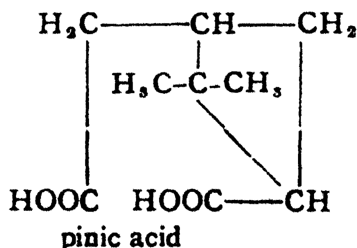


PINIC ACID.—It formed from α-pinonic acid by the action of bromine and alkali :—

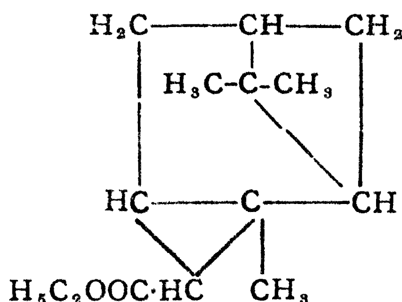


$$C_8H_{18}O_2CO{\cdot}CH_3 \xrightarrow[KOH]{Br_2} C_8H_{13}O_2.COOH + CHBr_3$$

· The $CO\text{-}CH_3$ group is replaced by $COOH$. The formation of bromoform indicates the presence of the methyl ketonic (CH_3—CO) group. Hence, pinic acid is :—

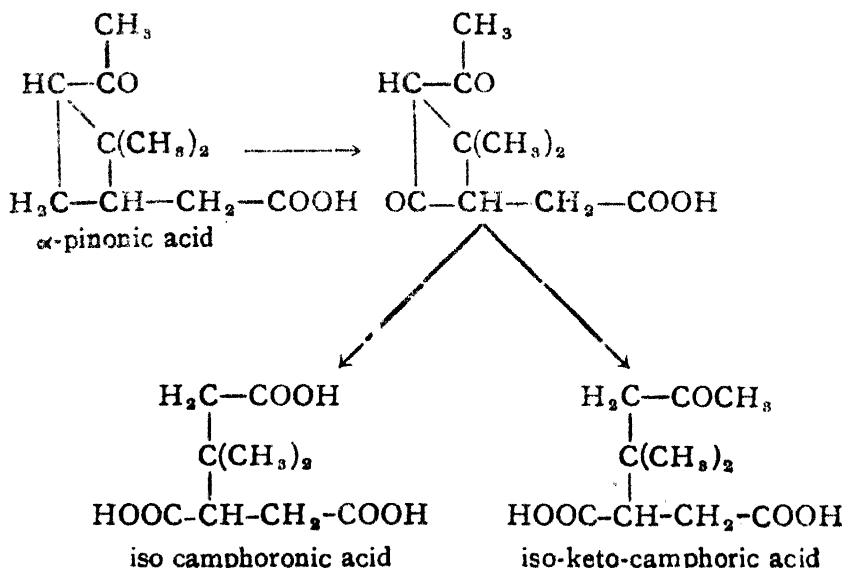


Pinene reacts with diazo-acetic ester to give a compound which has been assigned the structure :

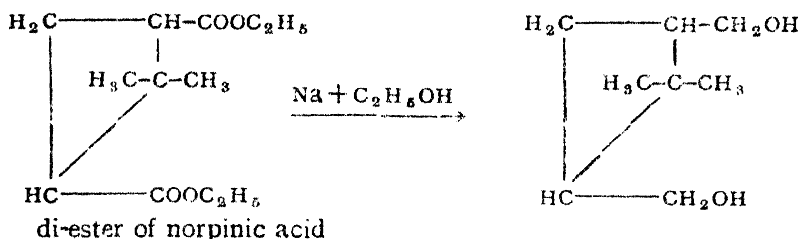


(This locates the double bond in pinene as between 1 and 2).

The above formula for pinene has been questioned, as it failed to account for the formation of iso-keto camphoric acid and iso-camphoronic acid by oxidation. However, the formation of these acids from α-pinonic acid and hence from pinene can be explained as follows :—

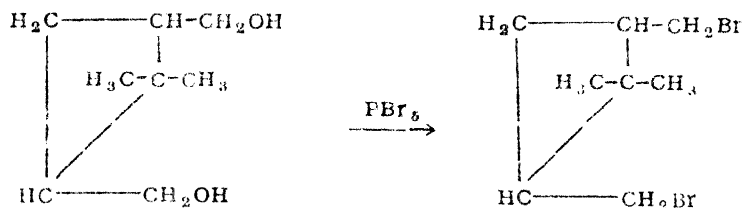


SYNTHESIS OF α-PINENE :—Ruzicka has accomplished a synthesis of α-pinene. The starting-point is norpinic acid, which is first converted into homo-pinic acid. The di-ester of norpinic acid is reduced with sodium and alcohol :—

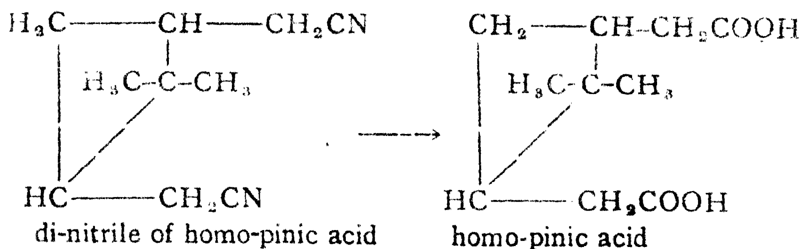


di-ester of norpinic acid

With phosphorus pentabromide, the corresponding di-bromo-derivative is formed.

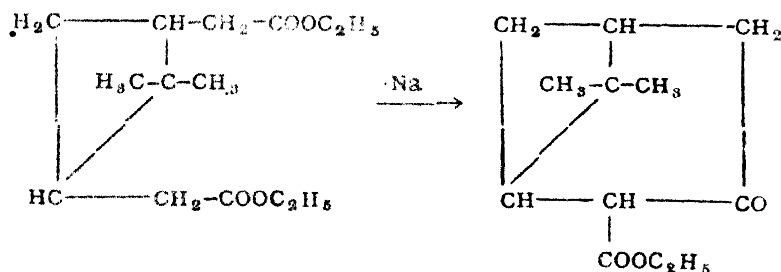


The di-bromo compound is then changed into the di-nitrile, which, on hydrolysis, gives homo-pinic acid.

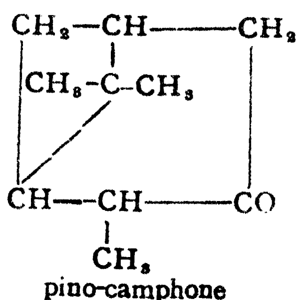


di-nitrile of homo-pinic acid homo-pinic acid

The diethyl-ester of homo-pinic acid is made to undergo internal condensation in the presence of metallic sodium. (Dieckmann's reaction).

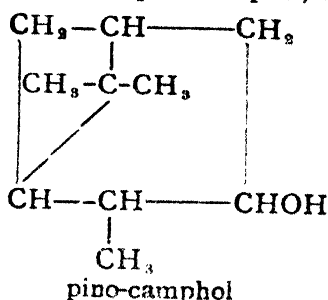


The keto ester is methylated with methyl iodide, and on hydrolysis and subsequent decarboxylation by heating, pinocamphone is formed.



pino-camphone

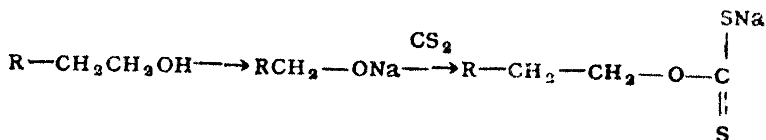
Pino-camphone is reduced to pino-camphol, with Na and alcohol.



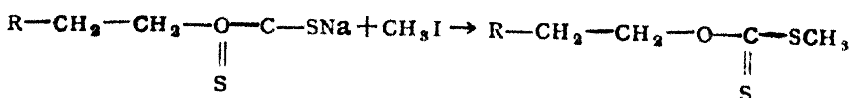
pino-camphol

The dehydration of pino-camphol to pinene cannot be effected with acid dehydrating agents, as the latter cause the cleavage of the cyclobutane ring.

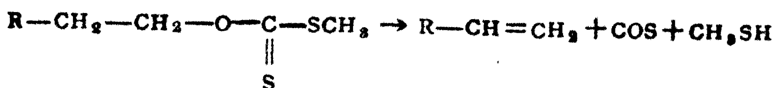
The methyl-xanthate of the above alcohol on distillation gives α pinene. Dehydration of an alcohol through the ester of xanthogenic acid was first discovered by Tschugaeff. The dehydration proceeds normally and no rearrangement reactions occur. The sodium derivative of the alcohol is treated with carbon disulphide to form the xanthogenic ester.



On methylation with methyl iodide or dimethyl sulphate, the methyl xanthate is obtained.



On distillation, it breaks down as follows :—

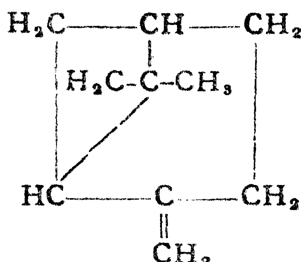


Similarly, pino–camphol would give α–pinene.

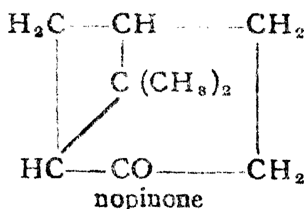
In another method, pinocamphone is converted into α pinene according to the following scheme :—

pino-camphone → oxime → pino-camphylamine → α–pinene.

β–Pinene or nopinene is a structural isomer of α-pinene. It has been assigned the following structure.



With $KMnO_4$, it gives successively a glycol, a hydroxy acid and finally a ketone, nopinone.



nopinone

USES OF PINENE :—Commercially it is used as the new material for the manufacture of synthetic camphor (q.v.). Also the affinity of α-pinene for hydrochloric acid or any halogen acid is so great that it can be used as a natural reagent to eliminate a molecule of the halogen acid.

CAMPHANE GROUP

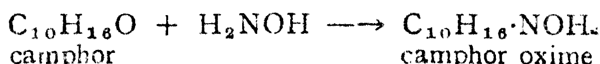
CAMPHOR is the most important member of the camphane group. It is very abundant and occurs widely distributed in nature, in the camphor tree in India, Japan and China. The chief constituent of oil of camphor obtained from the camphor tree, by steam distillation of the wood, leaves etc. is *d*-camphor. It is a crystalline solid m.p. 179°

......STRUCTURE OF CAMPHOR :—The determination of the structure of this compound presented such great difficulties that at one

time, no less than thirty different formulas had been proposed. All such formulas, however were based on very meagre experimental evidence such as the behaviour of the compound with dehydrating and dehydrogenating agents. The present structural formula of camphor is due to *Bredt* and rests on the studies of oxidative degradation products

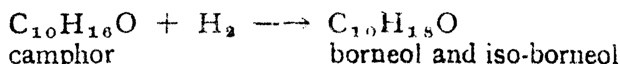
The molecular composition of camphor is $C_{10}H_{16}O$. It gives the following reactions :—

(*i*) That camphor is a *ketone* is indicated by the formation of :—(*a*) an oxime with hydroxylamine m.p. 119.5.



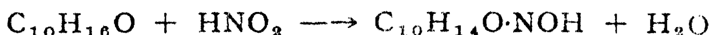
$$\underset{\text{camphor}}{C_{10}H_{16}O} + H_2NOH \longrightarrow \underset{\text{camphor oxime}}{C_{10}H_{16}{\cdot}NOH.}$$

and (*b*) of a mixture of secondary alcohols, borneol and isoborneol on reduction with sodium and alcohol.



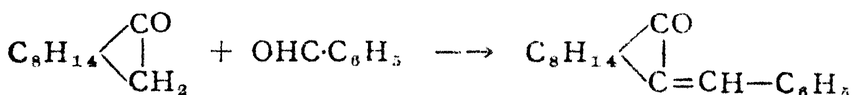
$$\underset{\text{camphor}}{C_{10}H_{16}O} + H_2 \longrightarrow \underset{\text{borneol and iso-borneol}}{C_{10}H_{18}O}$$

(*ii*) With amyl nitrite and hydrochloric acid, camphor gives an iso-nitroso (oximino) derivative.



$$C_{10}H_{16}O + HNO_2 \longrightarrow C_{10}H_{14}O{\cdot}NOH + H_2O$$

(*iii*) With benzaldehyde, a benzylidene derivative is formed :



$$C_8H_{14}\left\langle\begin{array}{l}CO\\ |\\ CH_2\end{array}\right. + OHC{\cdot}C_6H_5 \longrightarrow C_8H_{14}\left\langle\begin{array}{l}CO\\ |\\ C{=}CH{-}C_6H_5\end{array}\right.$$

Such reactions are characteristic of a reactive methylene group *i.e.* CH_2 group in proximity to a group like CO. Hence camphor must contain the group : CH_2—CO.

(*iv*) With bromine, camphor gives bromo camphor $C_{10}H_{15}OBr$, a substitution product, thus indicating that it is a saturated compound.

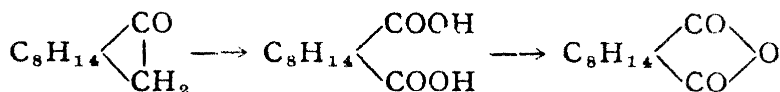
Thus the above reactions prove that camphor is a saturated ketone. The composition of an open-chain saturated ketone should be $C_{10}H_{20}O$, but camphor has the molar composition $C_{10}H_{16}O$. Hence it follows that camphor contains two cyclic systems.

(*v*) On heating with iodine, camphor is converted into carvarol *i.e.* 2-hydroxy-*p*-cymene. This indicates that the keto group is adjacent to the carbon atom carrying the methyl group and also

that camphor contains a six membered ring. This is further confirmed by the reaction of camphor with P_2O_5 or $ZnCl_2$.

(*vi*) When camphor is heated with P_2O_5 or $ZnCl_2$ at high temperature, *p*-cymene is formed.

NATURE OF THE CARBON FRAME WORK:—The most important evidence in the final elucidation of the structure of camphor is based on Bredt's studies on the oxidative degradation products. Bredt has shown that with nitric acid, camphor is first oxidised to a dibasic acid, camphoric acid, $C_8H_{14}(COOH)_2$. It is a crystalline compound m.p. 187°; it forms an anhydride (m.p. 227°) - it is optically active and exists in *six* stereo-isomeric forms.



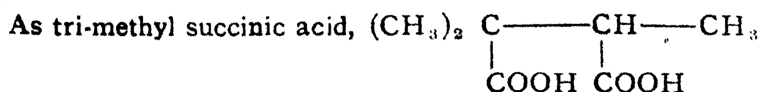
As the dibasic acid contains the same number of carbon atoms as the original ketone, it follows that the latter must be a cyclic ketone. Further, it is found that it is a dibasic acid of the cyclo-pentane system. This indicates that camphor contains a five membered ring. Camphoric acid, on further oxidation, gives a tribasic acid, camphoronic acid, $C_6H_{11}(COOH)_3$. The latter is a crystalline compound m.p. 137°. The constitution of camphor is deduced from that of camphoronic acid.

CONSTITUTION OF CAMPHORONIC ACID.—It is a tribasic acid closely resembling tri-carballylic acid. It is relatively stable as it can be distilled without decomposition, under reduced pressure. Hence, the three carboxylic groups in the molecule must be attached to three different carbon atoms.



On distillation, camphoronic acid decomposes into :—

(*a*) tri-methyl succinic acid, (*b*) iso-butyric acid, (*c*) carbon dioxide and (d) carbon.



is one of the products of decomposition, camphoronic acid must be represented by :—

$$\begin{array}{ccccc} & & CH_3 & & \\ & & | & & \\ (CH_3)_2C & \text{———} & C & \text{———} & CH_2 \\ | & & | & & | \\ COOH & & COOH & & COOH \end{array}$$

i. e., it is α–α–β trimethyl-tri-carballylic acid. The above structure can readily account for the observed decomposition products.

(*a*) A molecule of camphoronic acid may suffer oxidation to give tri-methyl succinic acid, as follows :—

$$\begin{array}{cccccc} & & CH_3 & \vdots & & \\ & & | & \vdots & & \\ (CH_3)_2C & \text{– – –} & C & \text{——}\vdots\text{——} & CH_2 & \\ | & & | & \vdots & | & \\ COOH & & COOH & \vdots & COOH & \\ & & & \downarrow & & \end{array}$$

$$\begin{array}{ccccc} & CH_3 & & & \\ & | & & & \\ (H_3C)_2C\text{———} & C\text{—}COOH & & HOOC\text{—}CH_2 & \\ | & | & + & | & \\ COOH & COOH & & COOH & \end{array}$$

$$\begin{array}{ccccc} & CH_3 & & & \\ \downarrow & | & & \downarrow & \\ (CH_3)_2C\text{———} & CH + CO_2 & & CH_3COOH + CO_2 & \\ | & | & & & \\ COOH & COOH & & & \end{array}$$

tri-methyl succinic acid

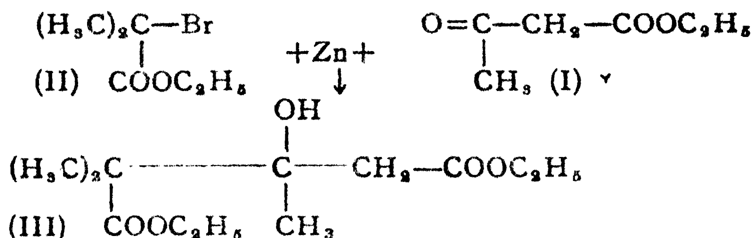
(*b*) Yet, another molecule of camphoronic acid may be oxidised to give isobutyric acid : ......

$$\begin{array}{ccccc} & & CH_3 & & \\ & & | & & \\ (CH_3)_2C & \text{————} & C & \text{– – –} & CH_2 \\ | & \vdots & | & & | \\ COOH & | & COOH & & COOH \\ & \downarrow & & & \end{array}$$

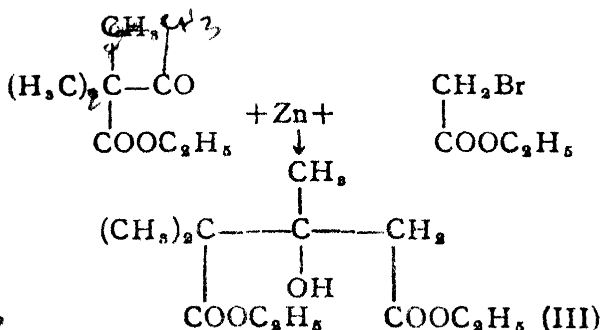
$$\begin{array}{ccccc} & & & CH_3 & \\ & & & | & \\ (CH_3)_2C\text{—}COOH & & HOOC\text{—} & C\text{– – –} & CH_2 \\ | & + & & | & | \\ COOH & & & COOH & COOH \\ \downarrow & & & \downarrow & \\ (CH_3)_2CH\text{—}COOH & & & (CH_3)_2CH\text{—}COOH & \\ \text{iso-butyric acid} & & & \text{iso-butyric acid} & \end{array}$$

SYNTHESIS OF CAMPHORONIC ACID :—A total synthesis of camphoronic acid by Perkin and Thorpe confirms the above structure. The synthesis consists in the condensation of acetoacetic ester (I)

with α-bromo-iso-butyric ester (II) in presence of zinc (Reformatsky's reaction) to form β-hydroxy tri-methyl glutaric ester (III).

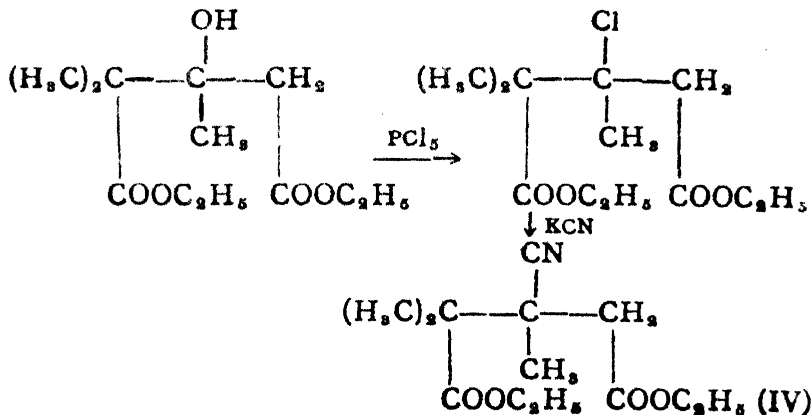


Or dimethyl-acetic ester is condensed with mono-bromo acetic ester in presence of zinc to form the β-hydroxy tri-methyl glutaric ester.

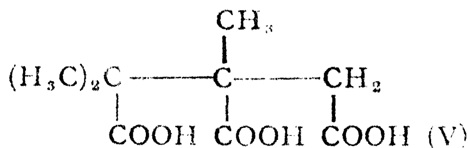


The β-hydroxy-tri methyl glutaric ester is then converted into camphoronic acid in the following way :—

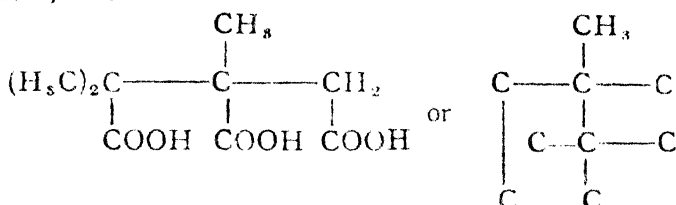
The hydroxyl group is replaced by chlorine atom by treatment with phosphorus pentachloride and then by cyano group by boiling with alcoholic potassium cyanide, to form the nitrile ester (IV) of camphoronic acid :—



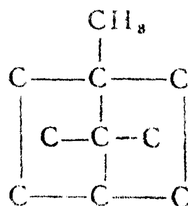
On hydrolysis, the cyano group is converted into a carboxyl group giving camphoronic acid, (V) :—(The ester groups also undergo hydrolysis).



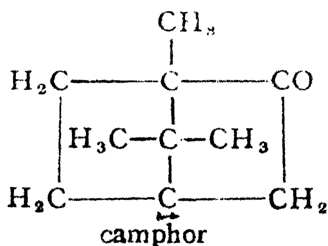
CARBON SKELETON IN CAMPHOR :—Now as camphoronic acid is formed from camphoric acid, the latter must have the same carbon skeleton, *viz.* :—



Hence, camphor must contain the same skeleton, but camphor contains ten carbon atoms. The tenth carbon atom must be so placed as to form a six-membered ring.



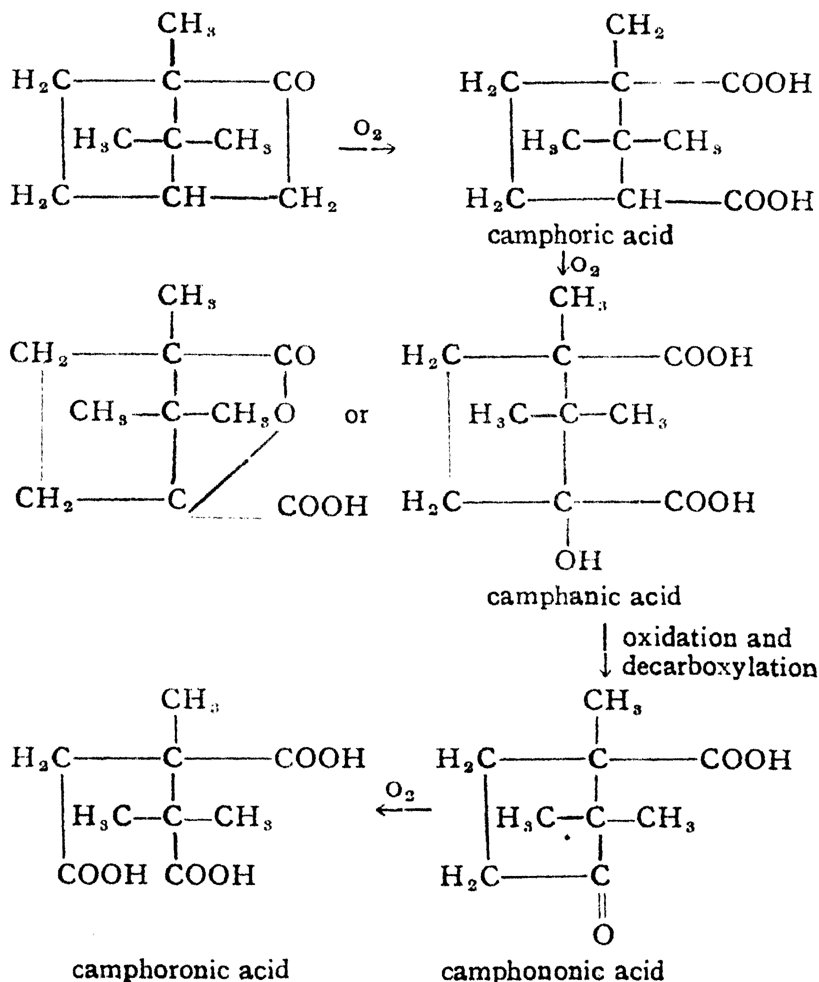
because camphor is converted into an aromatic derivative like *p*-cymene or carvacrol, under the influence of various reagents. Now, camphor is a saturated ketone, with the grouping CH_2-CO and the position of the keto group is indicated by the conversion of camphor into carvacrol *i.e* it is adjacent to the carbon atom carrying the methyl group. Hence, we have :—



camphor

This was the formula first proposed by Bredt. It readily accounts for:—(*a*) the ketonic nature of the molecule; (*b*) the presence of the CH_2-CO grouping; (*c*) the presence of a six-membered ring; (*d*) the presence of a five-membered ring.

The behaviour of the molecule on oxidation to form successively camphoric acid, camphanic acid, camphononic acid and camphoronic acid, is also satisfactorily accounted for :—

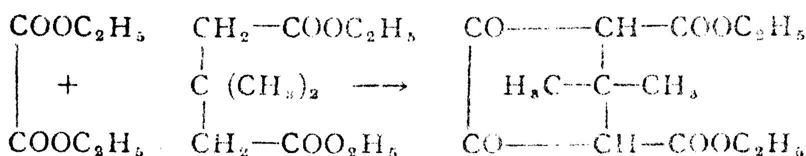


SYNTHESIS OF CAMPHOR:—Finally, the above structure has been confirmed by a synthesis. It consists of two parts: (*a*) synthesis of camphoric acid and (*b*) conversion of camphoric acid into camphor.

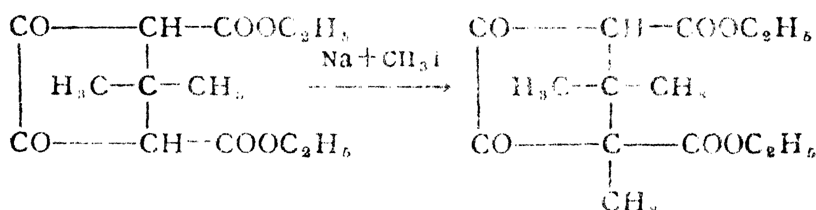
Komppa, Perkin and Thorpe have achieved a total synthesis of camphoric acid and by Haller's method, the latter thus has been converted into camphor.

(*a*) KOMPPA'S SYNTHESIS: The essential steps in the synthesis are :—

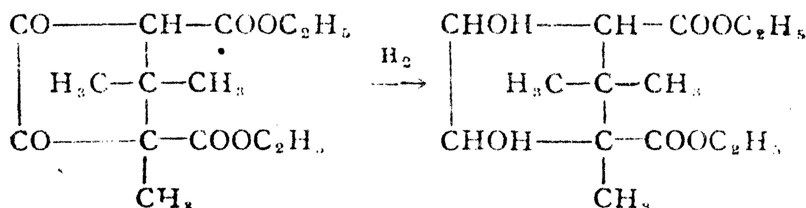
(*i*) Ethyl oxalate is condensed with β–β dimethyl glutaric ester in presence of sodium ethoxide to form di-keto apocamphoric ester. The β–β dimethyl glutaric acid is obtained from acetone, cyano acetic ester and ammonia (Guareshi–imide synthesis). It is also obtained from dimedone by oxidation with NaOBr.



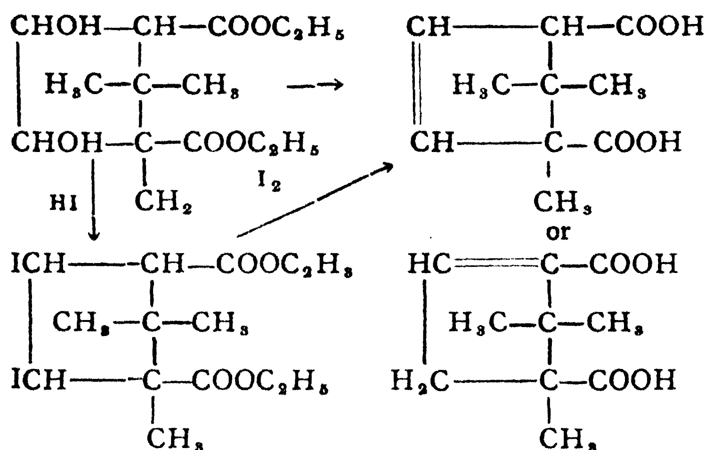
(*ii*) The latter, on methylation with sodium and methyl iodide, is converted into diketo-camphoric ester.



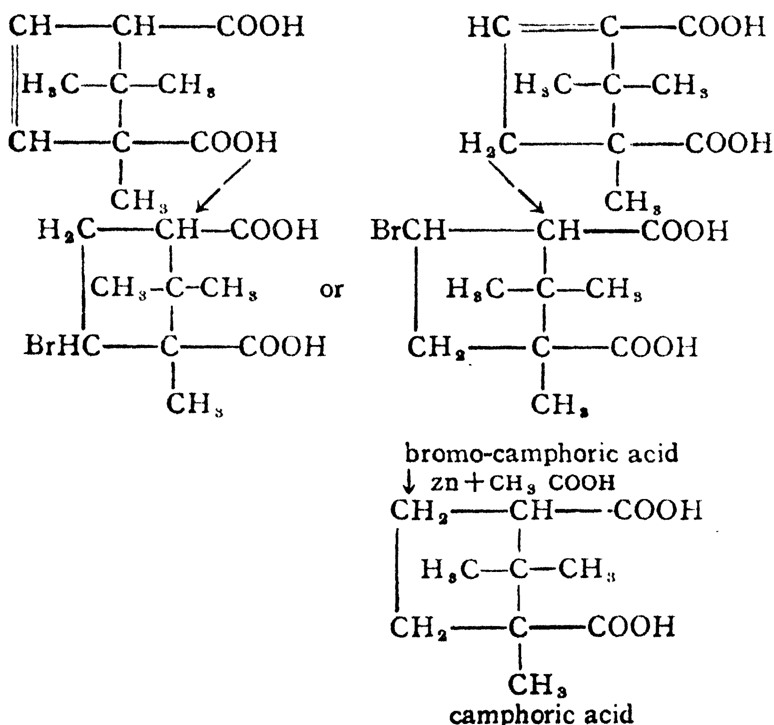
(*iii*) The diketo camphoric ester dissolved in sodium carbonate was reduced by sodium amalgam in an atmosphere of carbon dioxide; the two keto groups were thus reduced and dihydroxy camphoric acid ester was obtained.



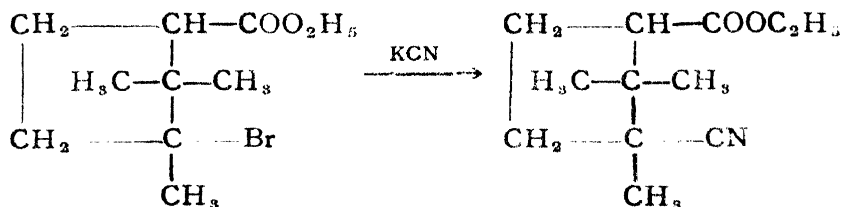
(*iv*) The latter, on boiling with hydriodic acid and red phosphorus, suffers reduction and dehydration to yield dehydro-camphoric acid.



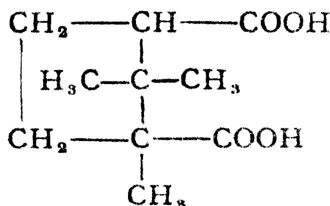
(*v*) The dehydro-camphoric acid was heated with hydrobromic acid solution at 125° to form bromo-camphoric acid, which, on reduction with zinc dust and acetic acid, gives inactive camphoric acid.



(*b*) In the sythesis of camphoric acid by Perkin and Thorpe, tri-methyl (1, 2, 2)–bromo (1)–cyclo-pentane carboxylic ester is used as the starting-point. It is treated with a mixture of potassium cyanide and hydrocyanic acid solution to form camphoric acid nitrile:—

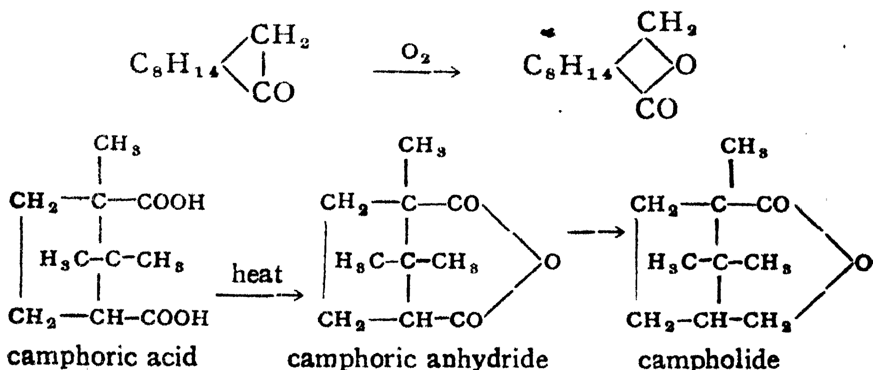


On hydrolysis, *dl*-camphoric acid is formed.



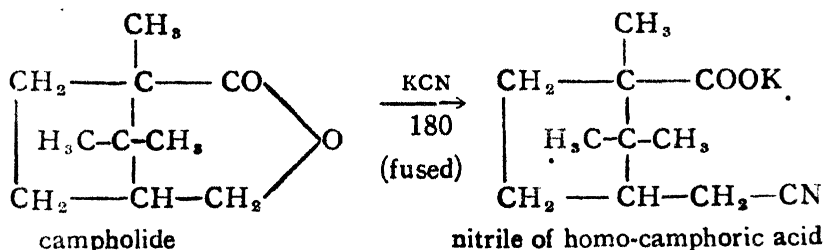
dl-camphoric acid

The camphoric acid thus obtained is then converted into camphor, by the Haller's method. The camphoric anhydride from camphoric acid, is reduced to campholide with sodium amalgam. The less hindered of the two carbonyl groups is reduced. Campholide is also obtained by the action of Caro's acid on camphor. This is a reaction characteristic of cyclic ketones.



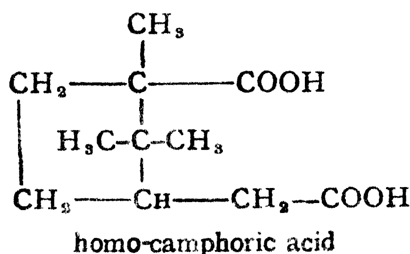
camphoric acid camphoric anhydride campholide

Campholide is then converted into the nitrile of homocamphoric acid by the action, of potassium cyanide.

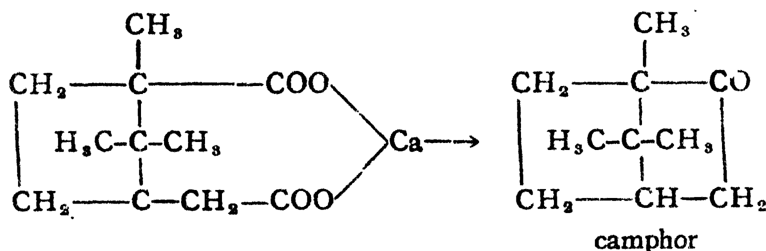


campholide nitrile of homo-camphoric acid

On hydrolysis with 50% H_2SO_4 homo-camphoric acid is formed

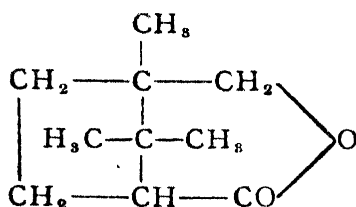

homo-camphoric acid

When the lead or calcium salt of the above acid is distilled the corresponding ketone, camphor, is obtained.

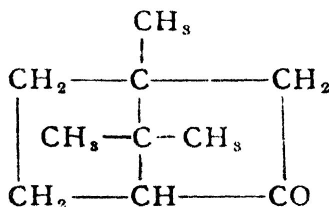

camphor

Blanc has reported the conversion of home-camphoric acid into camphor by the action of acetic anhydride. This is in agreement with his rule.

The conversion of camphoric anhydride into campholide may take place in such a way that the keto group adjacent to the $C—CH_3$ group (instead of CH) is reduced, giving campholide of the structure :—



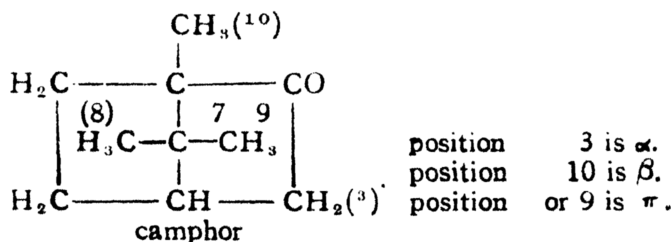
However, campholide of the above structure would be converted into a ketone, which would possess the formula :—



It is a ketone isomeric with camphor and not identical with it. Actually, campholide is obtained by reduction with Na-amalgam, is converted into camphor. Hence the conversion of camphoric anhydride into campholide must involve the reduction of the *CO* group, adjacent to—CH—group.

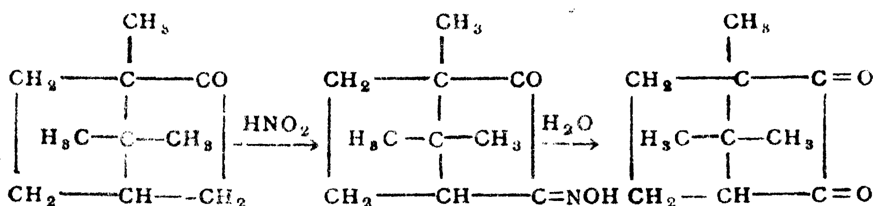
A few derivatives of camphor have been of some practical importance in analytical work. They are (*i*) the sulphonic acid derivatives and (*ii*) the quinone.

SULPHONIC ACID DERIVATIVES :—Camphor-sulphonic acid and bromo-camphor-sulphonic acid are important derivatives of camphor and are used for the resolution of racemic bases into their optically active isomerides; α, β and π derivatives are the most common.



α-Acid is prepared by the action of $Cl\text{-}SO_3\text{-}CH_3$ on camphor: β acid is obtained by the action of H_2SO_4 in acetic anhydride; π acid is obtained by the action of oleum or chloro-sulphonic acid.

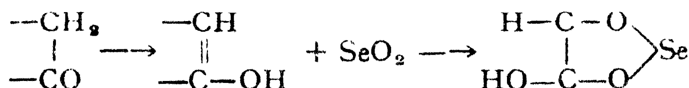
CAMPHOR QUINONE :—With nitrous acid (amyl nitrite and sodium ethoxide) camphor gives an iso-nitroso derivative which, on hydrolysis, gives camphor quinone.



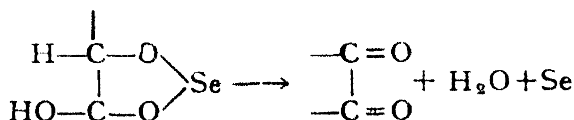
Recently, it has been found possible to oxidise camphor to camphor quinone by means of selenium dioxide, SeO_2, in toluene. The reagent is very valuable for the conversion of a methylene group adjacent to a carbonyl group in a keto group.



Its action is highly specific like that of an enzyme. The probable mode of attack by the reagent is that it adds to the enolic double bond, formed by enolisation.

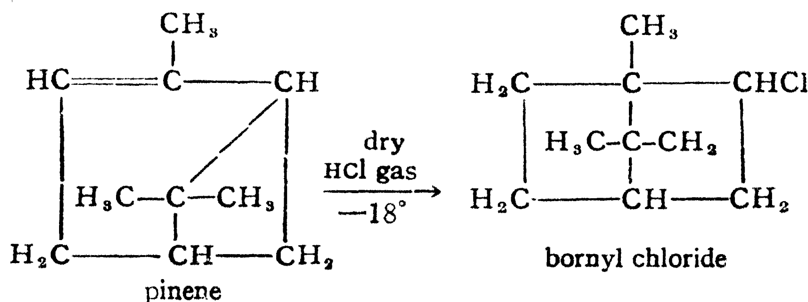


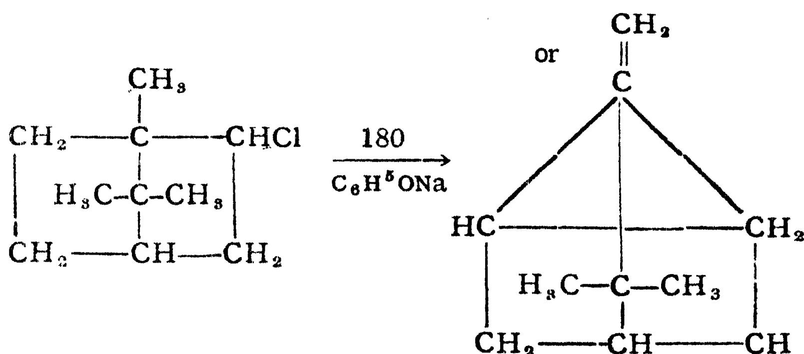
which then splits off water and selenium to give the diketone.

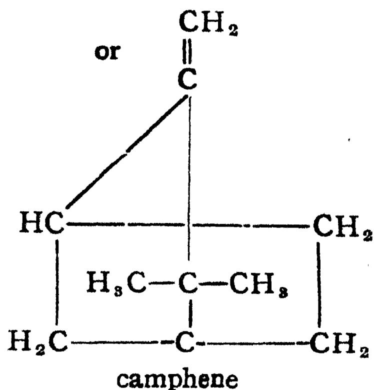


COMMERCIAL SYNTHETIC CAMPHOR :—Camphor is technically an important compound and recently, large quantities of it are obtained synthetically from oil of turpentine. α-Pinene, the chief constituent of the oil is converted into camphor by a number of methods. Technically, the most important ones are the following :—

(*a*) Pinene is converted into bornyl chloride by the action of dry hydrochloric acid gas. This change involves the opening up of the cyclo-butane ring and the formation of a cyclo-pentane ring. Bornyl chloride is then changed into camphene.

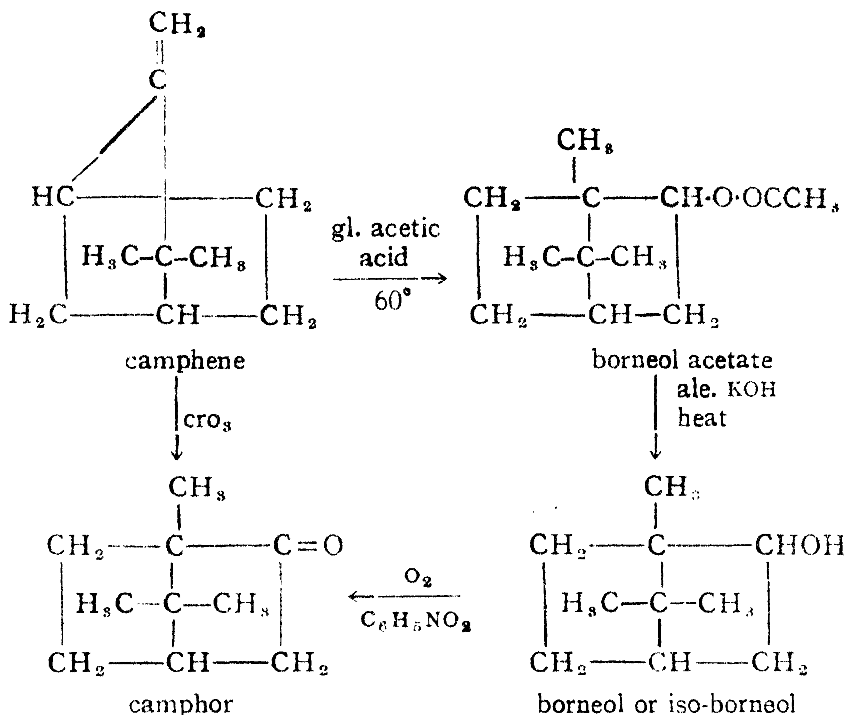






Camphene is then changed into camphor by one of the following methods :—(*i*) On treatment with a mixture of glacial acetic

acid and sulphuric acid, camphene is changed into a mixture of borneol and iso-borneol acetates. The mixture of the alcohols, obtained on hydrolysis, gives camphor on oxidation with nitrobenzene in alkaline conditions.

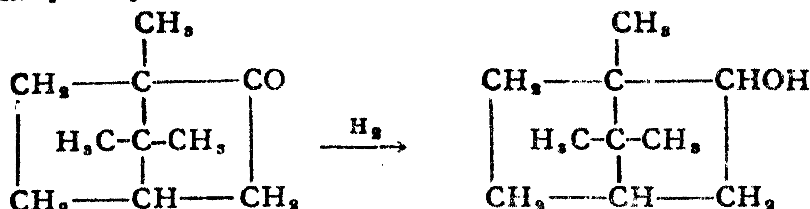


(*ii*) the camphene obtained from bornyl chloride is directly oxidised to camphor by chromic acid.

(*b*) Pinene is treated with an organic acid like acetic acid, when borneol acetate is directly obtained. The acetate, on hydrolysis and subsequent oxidation, gives camphor, as in the above method.

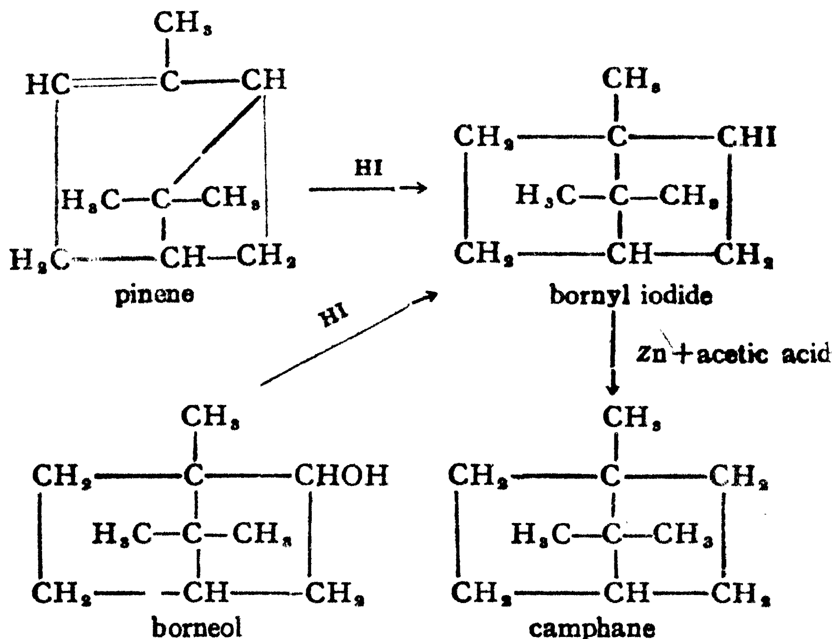
(*c*) In a more recent commercial method, pinene is isomerised to camphene, under mild conditions of temperature and in presence of TiO_2. The camphene is subsequently changed into iso-borneol-acetate by the action of sulphuric acid in acetic acid. The acetate is then hydrolysed to the alcohol, which is dehydrogenated catalytically to camphor. The dehydrogenation is effected in petroleum solution and in presence of oxides of metals like copper or Cu at 200°.

BORNEOL—$C_{10}H_{18}O$ is the secondary alcohol obtained from camphor by reduction with sodium and alcohol.



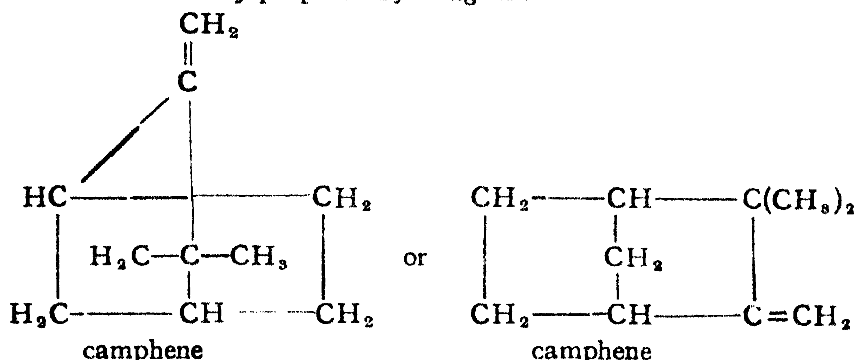
The product of reduction is usually a mixture of borneol and an isomeric alcohol, iso-borneol, They are probably stereoisomers; in borneol, the alcoholic hydroxyl is on the opposite side (trans) of the molecule from the *gem*-dimethyl group, while the hydroxyl of iso-borneol is close (cis) to that group.

CAMPHANE :—$C_{10}H_{18}$. This is the parent hydrocarbon of the camphane series. It does not occur in nature. It is readily obtained by the reduction of bornyl iodide, with zinc dust and acetic acid. Bornyl iodide is formed either from borneol or pinene by the action of hydriodic acid.



CAMPHENE :—$C_{10}H_{16}$ is the unsaturated hydrocarbon obtained by the dehydration of borneol with potassium bisulphate ($KHSO_4$) at 200°; or by heating bornyl halides with mild alkalies. The

problem of its constitution is still unsolved. The following srtucture has been tentatively proposed by Wagner :—



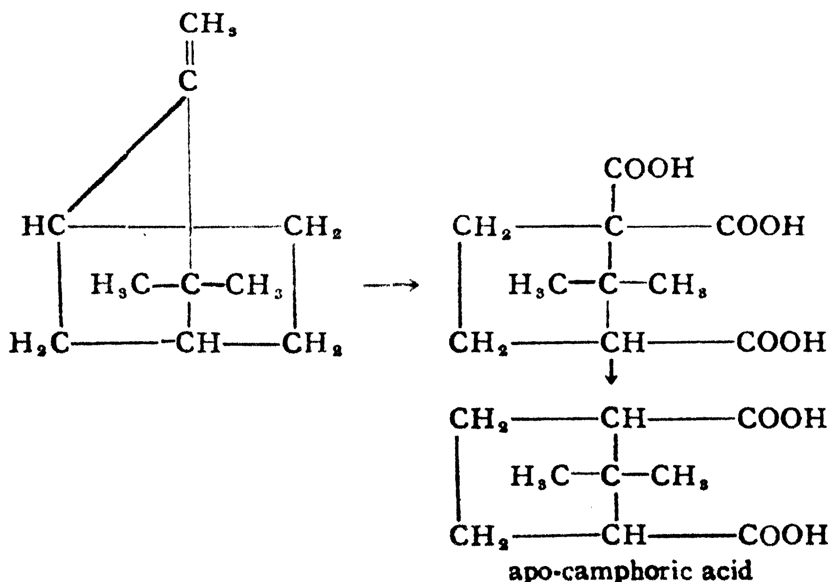
camphene camphene

Some of the typical reactions of camphene are :—

(*a*) Camphene, on oxidation with chromic acid. is converted into camphor. This reaction is the basis of the commercial manufacture of synthetic camphor. The change probably involves some rearrangement reactions.

(*b*) With acids, both mineral and organic, the corresponding bornyl and iso-bornyl derivatives are obtained (see p. 304).

(*c*) Oxidation with nitric acid, converts camphene into a tribasic acid, camphoic acid whicn on heating, loses carbon dioxide and gives apo-camphoric acid.



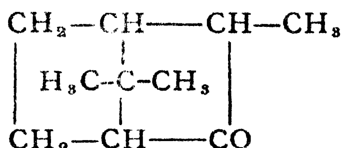
apo-camphoric acid

FENCHONE :—$C_{10}H_{16}O$ is a ketone isomeric with camphor. It occurs in *d* and *l* forms in nature. It resembles camphor closely but is distinguished from it by its greater resistance to oxidation. It gives the following reactions :

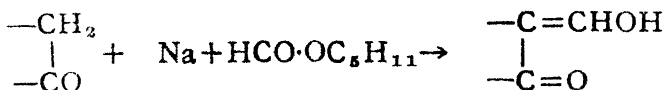
(*a*) On reduction, it gives a secondary alcohol, fenchyl alcohol; the latter, on treatment with phosphorus pentachloride, gives fenchyl chloride, which by the action of mild alkali, is converted into an unsaturated hydrocarbon, fenchene.

(*b*) Fenchene, on oxidation, is first converted into fencho-camphorone, $C_9H_{14}O$, which, by the action of nitric acid is decomposed into apo-camphoric acid.

These results indicate the presence of the same carbon skeleton as in camphor. Further, it is odvious that the methyl group in fenchone is placed in such a way that apo-camphoric acid (the lower homologue) instead of camphoric acid is formed. Hence, fenchone must be represented by the formula :

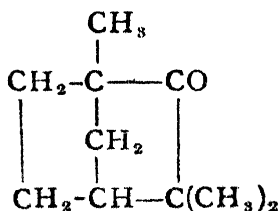


The above formula shows that fenchone contains no methylene group adjacent to a carbonyl group. This is proved by the reaction of fenchone with sodium and amyl formate. It has been shown by Claisen that ketones with the CH_2—CO—grouping are converted into oxy-methylene derivatives when acted upon by sodium and amyl formate.



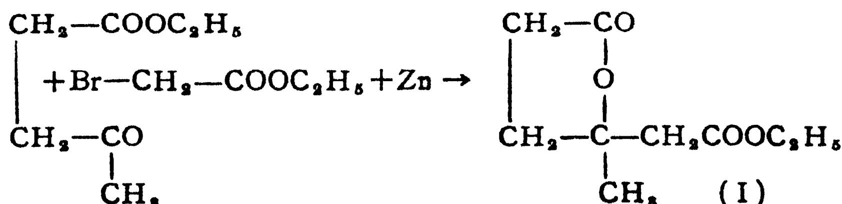
Fenchone gives no such oxy-methylene derivative, while camphor does.

Semmler has at the same time proposed that fenchone should be represented by :—

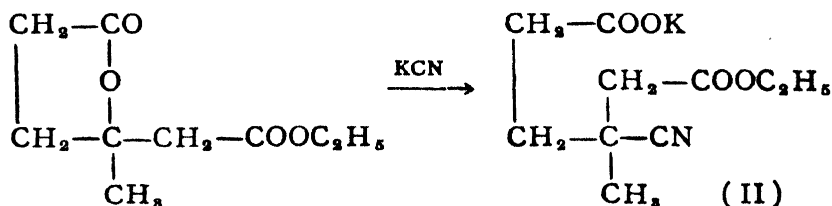


Recently, Ruzicka has obtained a satisfactory confirmation of Semmler's formula for fenchone by a complete synthesis of the compound. The essential steps in the synthesis are :—

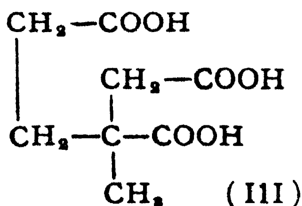
Levulinic ester is condensed with bromo-acetic ester in presence of zinc to form the lactonic ester (I).



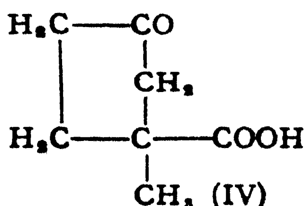
When heated with potassium cyanide, the lactone ester (I) is changed into the nitrile (II).



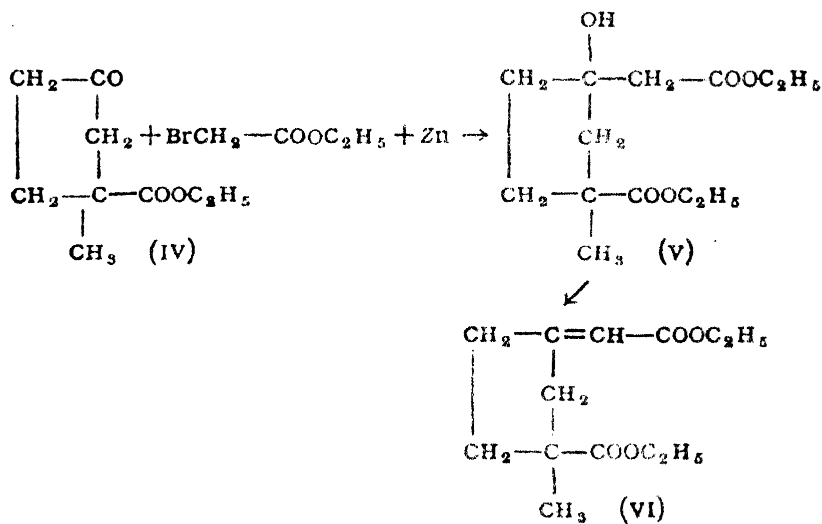
The latter, on hydrolysis, gives the tribasic acid (III).



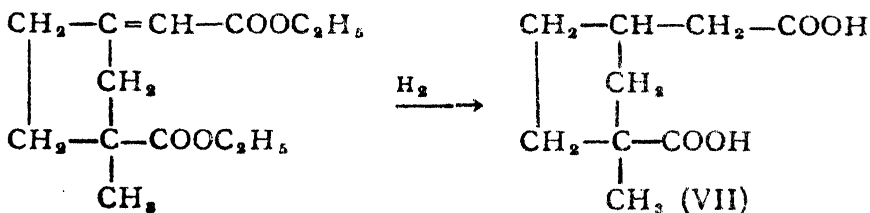
When heated with sodium and benzene, the tribasic acid (III) is converted into a penta-methylene derivative (IV).



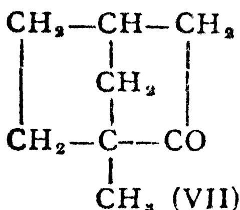
The ethyl ester of the acid is treated with bromo-acetic ester in presence of zinc when the hydroxy compound (V) first formed is partly dehydrated to the unsaturated compound (VI) :—



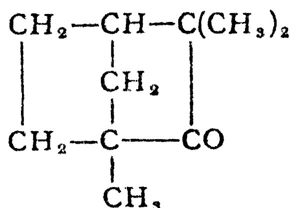
On reduction, the ester is changed into methyl-nor-homo-camphoric acid (VII).



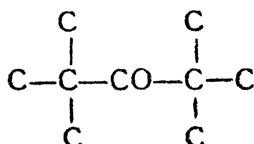
The distillation of the lead salt of (VII) yields methyl-nor-camphor (VIII).



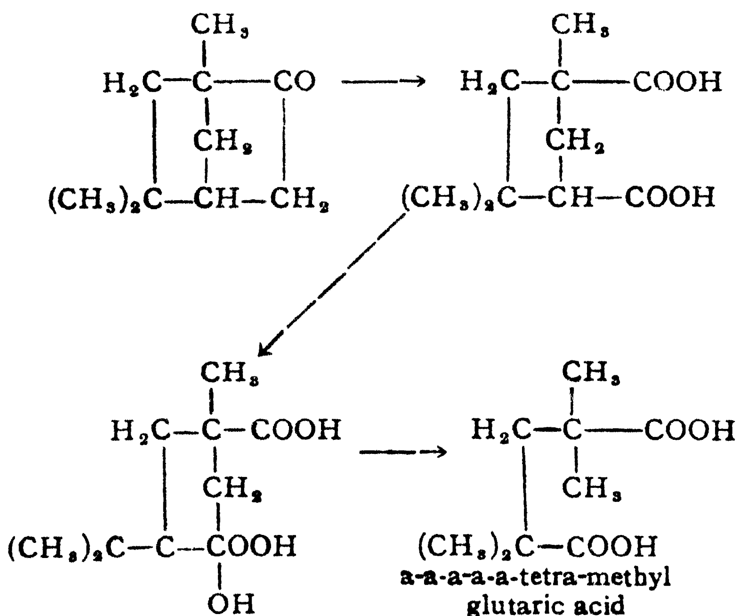
On methylation with methyl iodide, fenchone (IX) is formed : (the methylene group adjacent to the *CO* group is methylated).



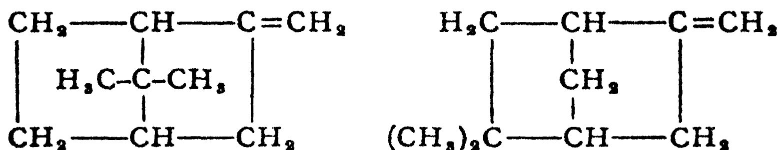
The greater resistance of fenchone towards oxidation is probably due to its carbonyl group being hedged in by two tertiary carbon systems :—



Iso-fenchone, on the other hand, is readily oxidised and is converted into α-α-α'-α'- tetra-methyl glutaric acid. Aschan, on the basis of the above results, has proposed the following structure for iso-fenchone which accounts for the known decomposition products:—



Fenchenes are the unsaturated hydrocarbons derived from fenchone and iso-fenchone The formation of these hydrocarbons from the corresponding alcohols obtained by reduction of the ketone, involves a rearrangement reaction. The fenchenes have been assigned the formulas :—



The above structures are based on the investigation of the oxidative degradation products of the molecules.

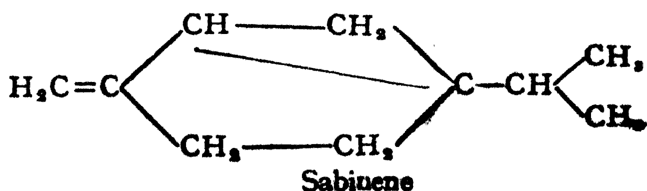
THUJANE GROUP

SABINENE is the most important member of this series. It occurs very widely in many essential oils *e.g.*, cedar wood oil, cardamom oil (Ceylon) and marjoram oil.

CONSTITUTION :—The molecular composition of sabinene is $C_{10}H_{16}$. Its structural formula is based on the following evidence :–

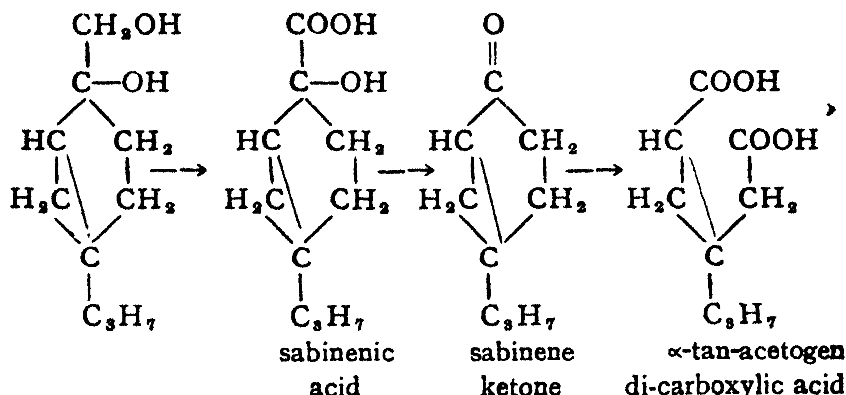
(y) *Relation to p–menthane* :—(*a*) with dilute sulphuric acid sabinene is converted into 1-4 terpin ; (*b*) hydrochloric acid changes sabinene dissolved in glacial acetic acid into 1-4 dichloro menthane. Hence, sabinene must be related to *p*–menthane.

(2) *Presence of cyclo-propane ring* :—The presence of a cyclopropane ring is proved by the behaviour of sabinene on oxidation. With potassium permanganate, it is successively oxidised to sabinenic acid, sabinene ketone, and finally to α-tanacetogen di-carboxylic acid, which is 1-isopropyl-2-carboxyl cyclo-propane-1-acetic acid. Sabinene is therefore to be represented by the formula :—

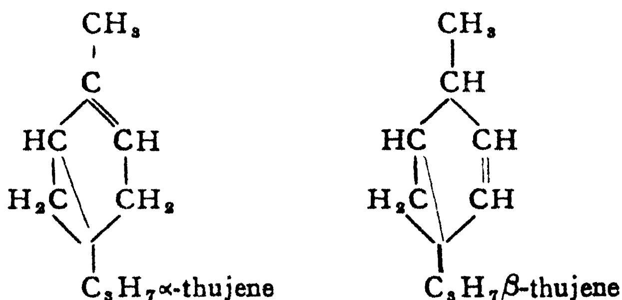


Sabinene

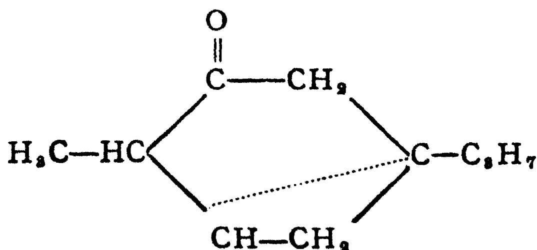
On oxidation, such a formula would give successively :



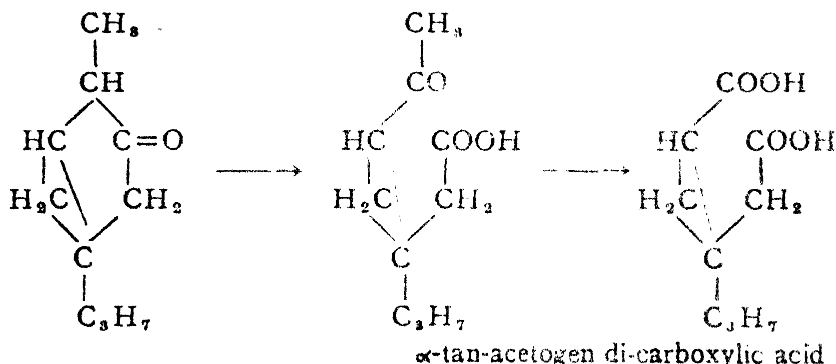
The conversion of sabinene into *p*-menthane derivatives can also be readily explained ; ∝ and β-thujenes are isomeric with sabinene.



Thujone is the ketone of the thujane series. It exists in two stereo-isomeric forms ∝ and β. (Difference is only in the configuration of carbon atom no. 1). Its structure is :—



On reduction, it is changed into thujyl alcohol. On oxidation with potassium permanganate, it gives ∝-tan-acetogen dicarboxylic acid.



∝-tan-acetogen di-carboxylic acid

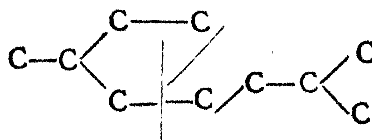
Olefinic Terpenes

Most of the valuable essential oils owe their aroma to compounds belonging to this class. The oils of rose, lavender, orange blossoms, lemon-grass and citronella, contain large quantities of substances called olefinic terpenes or terpinogens. They possess the molecular composition $C_{10}H_{16}$ or $C_{10}H_{16}O$ or $C_{10}H_{18}O$. They occur as hydrocarbons, alcohols, or aldehydes. They are isomeric with the mono and dicyclic terpenes, into which they are readily converted, but structurally they are open chain unsaturated compounds and hence the name olefinic terpenes. They are closely related to the cyclic terpenes into which they can be readily transformed. They contain ten carbon atoms, which are present in the molecule in such a way that :—

(*a*) six of them form a straight chain.

(*b*) three of them form an isopropyl group, and

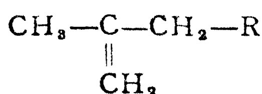
(*c*) one of them is present as a methyl group. The nature of the carbon framework present is :—



The olefinic terpene molecule is thus built up of two isoprene units and the skeleton closely resembles that of a monocyclic terpene in which the ring is opened up. The presence of such a system readily accounts for ease of transformation of the olefinic terpenes into: (*a*) *p*-cymene derivatives like terpineol and (*b*) tetra-hydro benzene derivatives *e.g.* α and β ionones. Conversion of citral into *p*-cymene, and of geraniol into terpineol are examples of the first type, while the formation of the ionones from citral represents cases of the second.

The isopropyl system in these terpenes may be present as either (*A*) or (*B*). It is very susceptible to acids or alkalis.





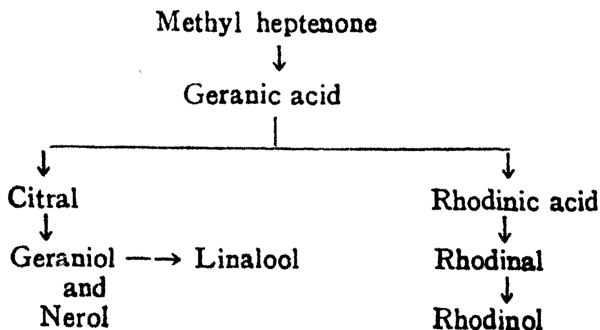
isopropylidene (*A*) isopropylene (*B*)

The naturally occurring terpenes as a class possess the isopropylidene end group. It is only during oxidative degradation that partial, rearrangement to isopropenyl system occurs.

ISOPRENE may be looked upon as the simplest olefinic terpene. It has the molar composition C_5H_8; it does not occur in nature; it is only a synthetic product. It is a liquid, b.p. 37°C.

THE CITRAL GROUP

Among the olefinic terpenes, the most common and important are citral, geraniol, nerol, rhodinol etc., which together constitute the 'citral group'. Structurally, they are related to an unsaturated ketone—*methyl heptenone* from which they can be readily derived. Methyl heptenone is a natural product but is of very little importance. The above relationships may be formulated as follows:—



Methyl heptenone :—It is found in many essential oils *e. g.* lemon-grass oil; it is obtained by boiling citral with a 10% aqueous solution of K_2CO_3. It is a liquid (b. p. 171°), which smells like flowers. Its constitution is based on the following evidence:—

(*i*) Its molecular composition is $C_8H_{14}O$.

(*ii*) It forms an oxime and a hydrazone.



$$C_8H_{14}O + H_2NOH \longrightarrow C_8H_{14}NOH.$$

Hence an aldehydic or ketonic group is indicated.

(*iii*) With Br_2, a dibromide is formed,

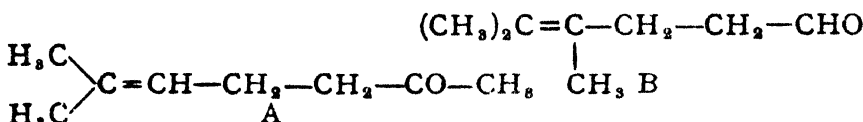


$$C_8H_{14}O + Br_2 \longrightarrow C_8H_{14}O{\cdot}Br_2$$

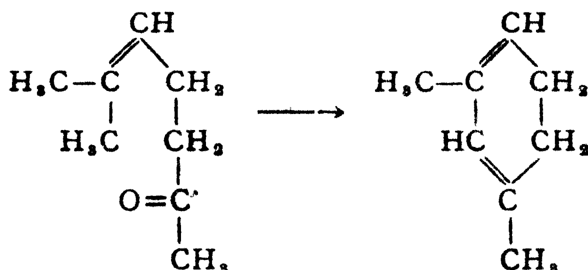
i.e. a double bond is present.

(*iv*) On oxidation with chromic acid, it gives (*a*) acetone and (*b*) levulinic acid, $CH_3CO{\cdot}CH_2CH_2COOH$.

The above reactions therefore lead to either of the two following formulas for methyl heptenone.

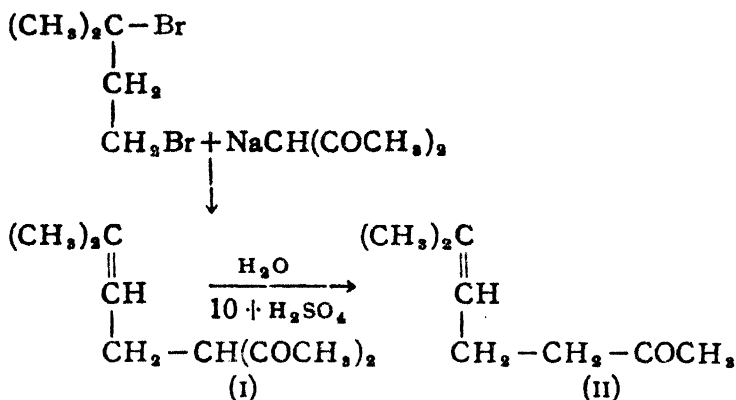


The structure A is assigned to methyl heptenone because on shaking with 75 per cent sulphuric acid it is converted into dihydro-*m*-xylene.



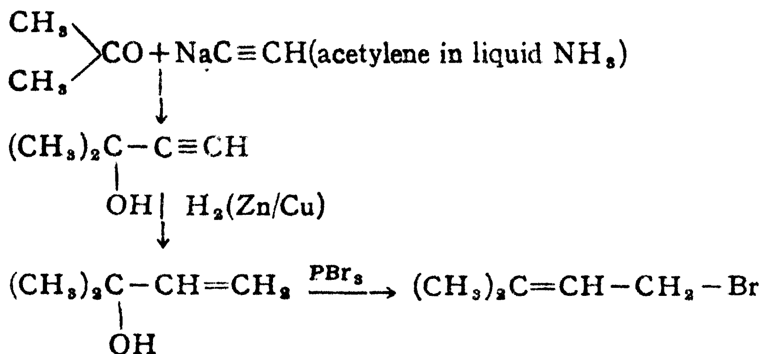
The structure B under these conditions would give di-hydro-ortho-xylene.

Synthesis :—A number of different syntheses of methyl heptenone have been accomplished. The synthesis by Barbier and Bouveault consists of the following :—2-methyl-2-4-dibromobutane is condensed with sodium derivative of acetyl acetone in alcohol. The unsaturated diketone (I) is first formed, which subsequently on boiling with alkali undergoes 'ketonic' hydrolysis to give methyl heptenone (II).



In the recent Ipatiew method, sodio-ethyl aceto-acetate is used in place of sodio acetyl acetone and the final hydrolysis is effected with $Ba(OH)_2$.

A simpler synthesis of methyl heptenone may be described :



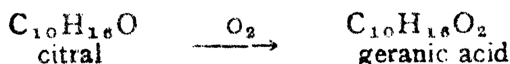
The latter on condensation with ethyl aceto-acetate and subsequent hydrolysis gives methyl heptenone.

CITRAL

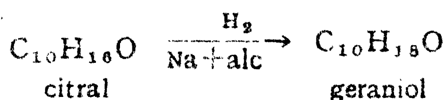
Citral is the most abundant of the naturally occurring olefinic terpenes; its chief source is the lemon-grass oil in which it is present to the extent of 70-80%. It is isolated from the oil in the form of its sodium-bisulphite addition product; the latter on hydrolysis gives citral. It is an oil with a strong lemon-like odour (b. p. 228°C). It is used in the preparation of ionones.

CONSTITUTION OF CITRAL :—The molecular composition is $C_{10}H_{16}O$. Its structural formula is based on the following *analitical* and *synthetical* evidence. Some important names associated with these investigations are Barbier, Bouveault, Semmler, Tiemann.

(*a*) Citral can be oxidised to geranic acid $C_{10}H_{16}O_2$, a monobasic acid containing the same number of carbon atoms.

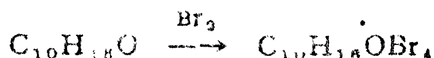


Hence, an aldehyde group is indicated. This is further confirmed by the reduction of citral to geraniol which is a primary alcohol.



Citral also forms an oxime, and an addition product with sodium-bisulphite. With excess of the latter, a disulphite addition product is formed. This indicates that there is a double bond in $\alpha\ \beta$ position to the *CHO* group.

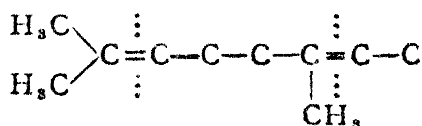
(*b*) *Nature of unsaturation* and *carbon-framework* :—Citral readily combines with bromine to form a tetra-bromide.



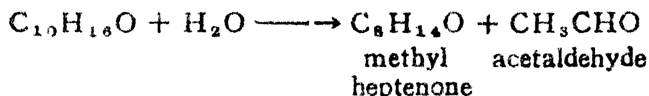
Citral therefore, must contain two double bonds. The position of the double bonds and the carbon-framework are established by oxidation reactions :—

Oxidation with chromic acid converts citral into :—(*i*) acetone, $CH_3—CO—CH_3$; (*ii*) levulinic acid, $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot COOH$; (*iii*) CO_2. Controlled oxidation with $KMnO_4$, gives methyl-heptenone, oxalic acid etc.

Now, as the oxidation of the molecule occurs at the position of the double bonds, with subsequent disintegration of the molecule at these points, it follows that the following chain of carbon atoms must be present in citral :—



On boiling with potassium carbonate solution, citral takes up one molecule of water and forms methyl heptenone and acetaldehyde. (This reaction is characteristic of an $\alpha\ \beta$ unsaturated aldehyde or ketone.

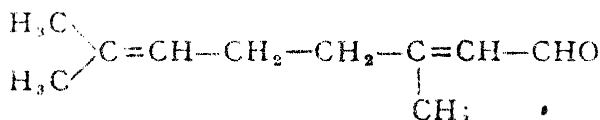


$$C_{10}H_{16}O + H_2O \longrightarrow C_8H_{14}O + CH_3CHO$$

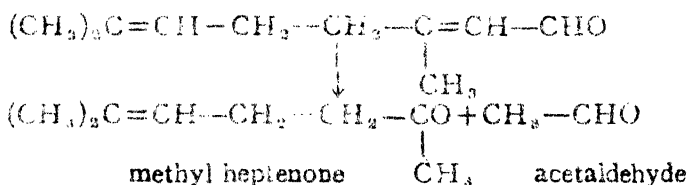
methyl heptenone   acetaldehyde

Probably, the elements of water are added across one of the two double bonds present. (This is the reversal of the aldol condensation).

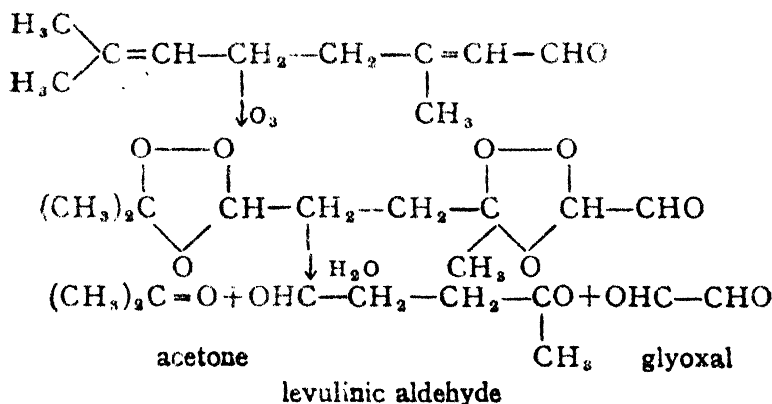
Hence it is obvious that the structure of citral is based on that of methyl heptenone. The latter is a ketone and citral an aldehyde, and citral on hydrolysis, gives methyl heptenone and acetaldehyde. It is probable that they are condensed as in aldol condensation. Hence, citral may be :—



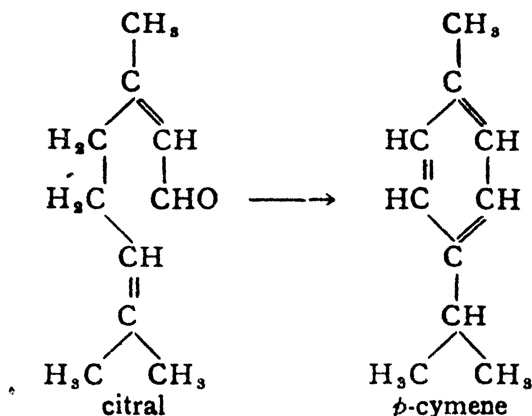
which would readily explain the hydrolysis of citral into methyl heptenone and acetaldehyde :—



Finally, the results of ozonolysis of citral, confirm the above structure. Citral forms a di-ozonide, $C_{10}H_{16}\cdot 2O_3$, thus indicating the presence of two double bonds. The diozonide, on hydrolysis, gives (*a*) acetone, (*b*) levulinic aldehyde and (*c*) glyoxal, which is in good agreement with the formula :—



The conversion of citral into *p*-cymene, by the action of strong acids or potassium hydrogen sulphate is readily accounted for, on the above formula :—

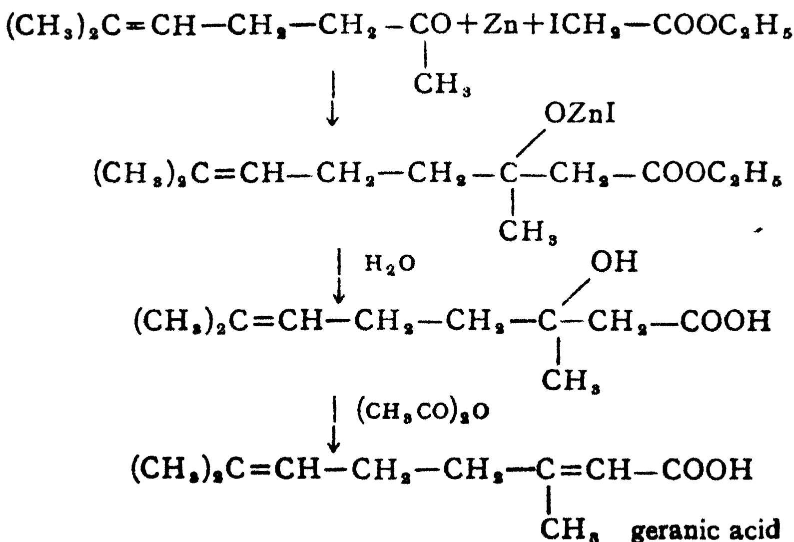


SYNTHESIS OF CITRAL :—A total synthesis of citral consists of three parts :—

(*a*) synthesis of methyl heptenone; (*b*) synthesis of geranic acid; (*c*) conversion of geranic acid into citral.

(*a*) For the synthesis of methyl heptenone (see p. 297).

(*b*) The synthetic methyl heptenone is then converted into geranic acid by condensation with iodo-acetic ester in presence of zinc. The different steps are :



(*c*) The calcium salt of geranic acid, on dry distillation with calcium formate, gives the corresponding aldehyde, citral or geranial.

$$(CH_3)_2C{=}CH{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH{-}COOCa' + HCOOCa'$$

$$\downarrow$$

$$(CH_3)_2C{=}CH{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH{-}CHO + CaCO_3$$

citral

Recently, a method for the conversion of methyl heptenone into citral has been reported. It consists of the following steps:—

$$(CH_3)_2\,C{=}CH{-}CH_2{-}CH_2{-}CO{-}CH_3 + Br\,Mg{-}C{\equiv}COC_2H_5$$

$$\downarrow$$

$$(CH_3)_2\,C{=}CH{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle OH}{\overset{|}{C}}}}{-}C{\equiv}C{\cdot}OC_2H_5$$

$$\downarrow H_2\ (Pd/c)$$

$$(CH_3)_2\,C{=}CH{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle OH}{\overset{|}{C}}}}{-}CH{=}CH{\cdot}OC_2H_5$$

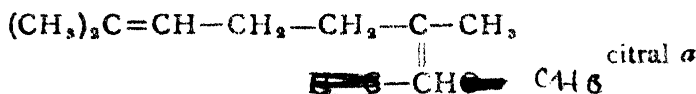
$$\downarrow HCl$$

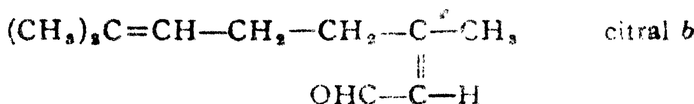
$$(CH_3)_2\,C{=}CH{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH{-}CHO$$

ISOMERS OF CITRAL:—Citral exists in three isomeric forms. There is the structural isomer (*A*) whose constitution differs from that of citral, in the position of one of the double bonds.

$$\begin{matrix}CH_3\\CH_2\end{matrix}\!\!>\!C{-}CH_2{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH{-}CHO \qquad (A)$$

Further, Harries and Himmelmann have reported the existence of geometrically isomeric forms in the case of citral. They are citral *a* and citral *b*.

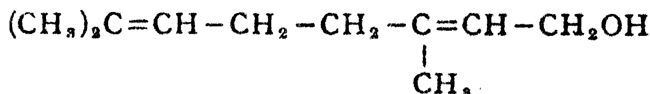




Citral *a* and citral *b* are structurally identical. The citral of commerce is probably a mixture of the two stereo-isomerides. The relative configurations of the *a* and *b* forms have been deduced from their relations to geraniol and nerol respectively.

GERANIOL AND NEROL :—They occur in oil of geranium, oil of rose, and eucalyptus oil. Geraniol is obtained in large quantities from citral, for the preparation of rose scents, by reduction with Alamalgam. On a commercial scale, it is obtained from the cheap natural oil of palmrosa or oil of citronella. The latter is treated with finely powdered anhydrous $CaCl_2$ and the mixture chilled to—5° and kept for severnl hours. Geraniol present in the oil, forms a crystalline adduct which separates out. The adduct is then decomposed with water to give geraniol. Both geraniol and nerol are liquids ; geraniol boils at 229-30°; and nerol at 225-226°. Geraniol on being heated with alcoholates is converted into nerol.

CONSTITUTION OF GERANIOL AND NEROL :—Both have the same molecular composition $C_{10}H_{18}O$, and are formed readily from citral by reduction with Na and alcohol. They thus represent two isomeric primary alcohols. They are separated from each other by the action of $CaCl_2$; geraniol forms a crystalline addition product with it while nerol does not ; geraniol on catalytic reduction gives citronellol and with H_3PO_4, HCl gas, dipentene is formed. Further, it can be readily proved by oxidation reactions that they are structurally identical, and possess the formula :—



Hence, they are stereo-isomers; and as there is no asymmetric carbon atom, probably they are geometric isomers. The relative configurations have been established by the following considerations: Both geraniol and nerol, under the influence of acetic acid containing one or two per cent sulphuric acid, are converted into α-terpineol:—

```
        CH3                                   CH3
        |                                     |
        C                                     C
       / \\                                  / \\
   H2C     CH                            H2C     CH
    |      |                              |      |
   H2C     CH2OH        ——→              H2C     CH2
      \                                     \   /
        CH                                    CH
        ‖                                     |
        C                                     C—OH
       / \                                   / \
   H3C     CH3                           H3C     CH3
   geraniol or nerol                      α-terpineol
```

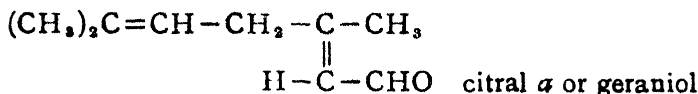
But nerol reacts nine times as fast as geraniol and the transformation involves the closing up of a six-membered ring. An inspection of the two possible geometric isomers (*A*) and (*B*),

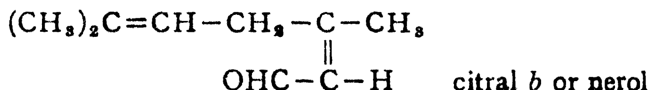
```
      (CH3)2C=CH-CH2-CH2-C-CH3
            ↖*           ‖
(A)                    H-C-CH2OH

      (CH3)2C=CH-CH2-CH2-C-CH3
            ↖*           ‖
(B)                 HOH2C-C-H
```

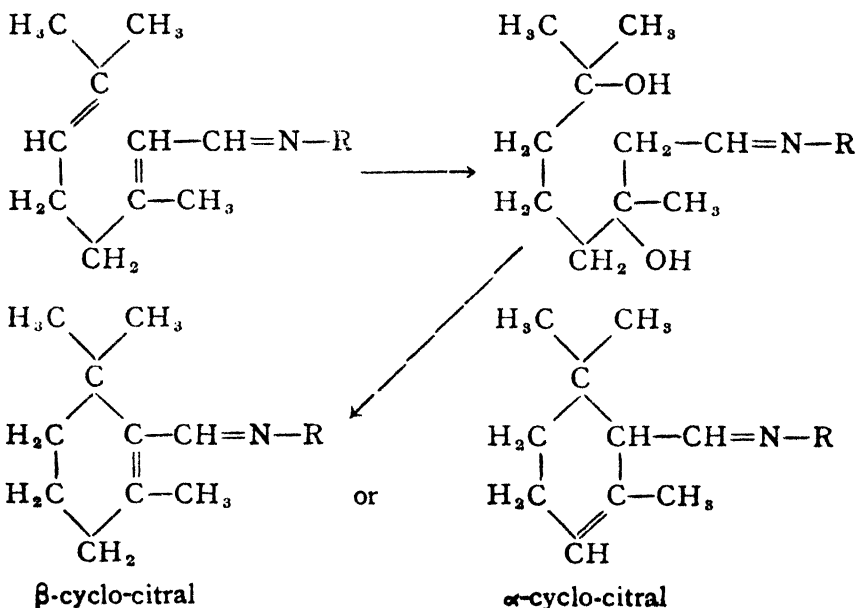
will show that in (*A*), the carbon atom carrying the hydroxyl, and one marked with an asterisk, which are involved in the ring closure, are further apart than they are in (*B*). Hence, ring closure would occur more readily with (*B*) than with (*A*). Nerol, therefore, must be represented by (*B*) and geraniol by (*A*).

The configurations of citral *a* and citral *b* are then deduced as follows:—On oxidation, geraniol gives a mixture of citral *a* and citral *b* in which the former preponderates. On the other hand, nerol forms predominantly the *b* isomer. Hence, we may conclude that citral *a* has the same configuration as in geraniol while citral *b*, as in nerol.



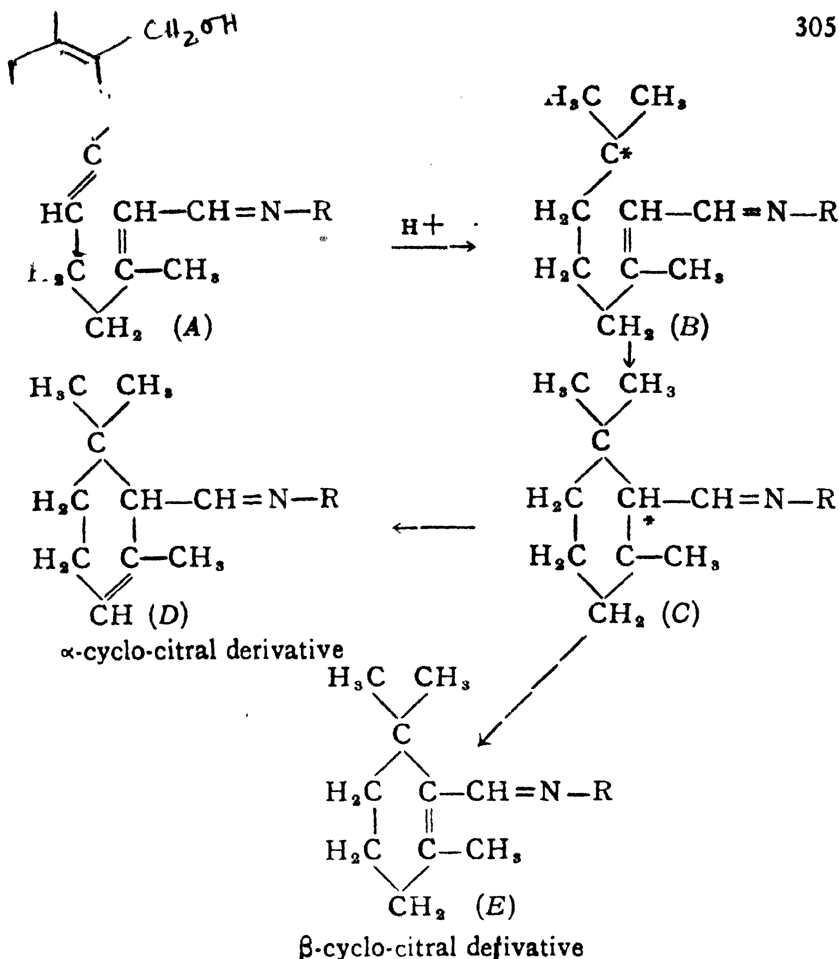


CYCLO-CITRALS :—We have already seen that citral can be converted into cyclic compounds like *p*-cpmene, by internal condensation with strong acids. This probably involves the aldehyde group because there is still a second type of condensation reaction which takes place with a citral derivative in which the aidehyde group is blocked. Thus, we have with the azo-methine derivative of citral, two isomeric cyclo-citral derivatives.



β-cyclo-citral α-cyclo-citral

It was believed that a hydrated intermediate product was first formed, which suffered cyclisation and elimination of water. The dehydration took place in two ways giving rise to two isomeric cyclo-citrals, α and β. However, it is now held that the cyclisation of the citral derivative is a case of internal cyclisation of a di-ene under the influence of H^+ ions.



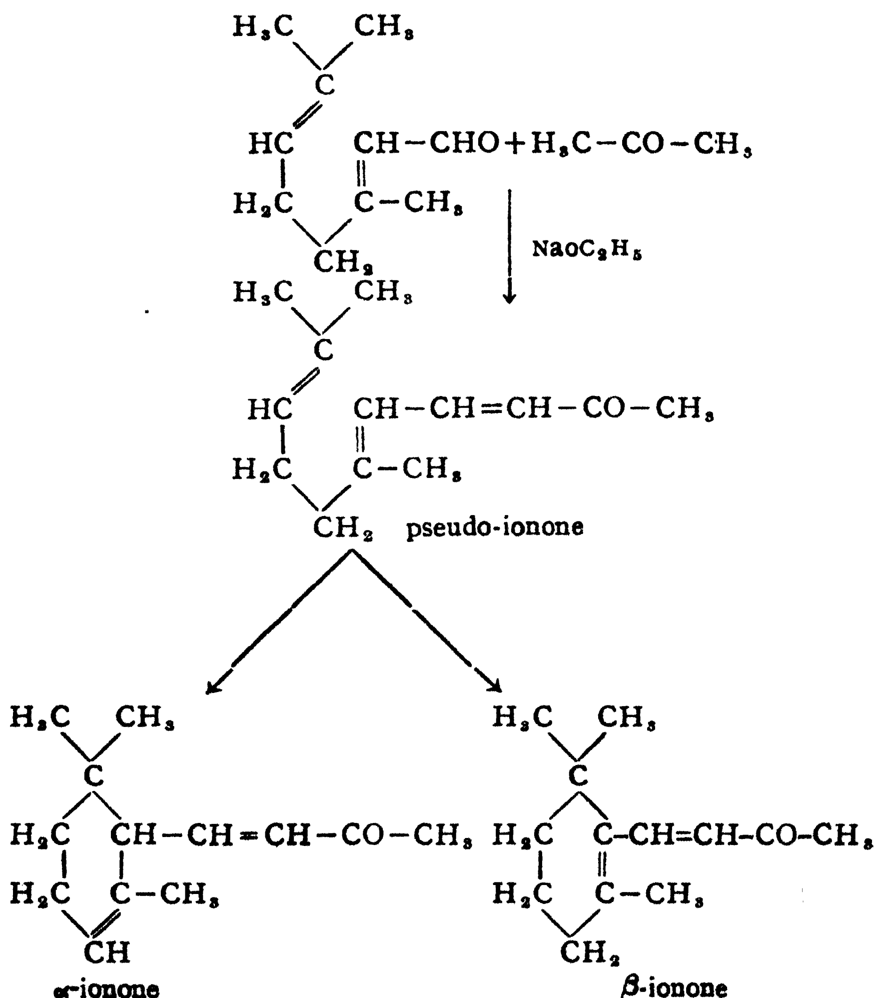
α-cyclo-citral derivative

β-cyclo-citral derivative

The carbon atom marked with an asterisk in (*B*), carries only *six* electrons and is capable of readily uniting with a carbon atom bound by a double bond. Thus, the ring closure is effected as in (*C*) and a new carbon atom with *six* electrons appears. The whole structure is then *stabilised* by the loss of one H^+ ion. This may occur in two ways so as to give (*D*) and (*E*).

α AND β-IONONES :—Two important derivatives of cyclo-citrals which are of great commercial interest, are the α-and β-ionones. They are synthetic products and so they have not been found in nature. They form the basis of artificial violet essence. In dilute solutions they possess the characteristic odour of violets. β-ionone is also used in the synthesis of vitamin A.

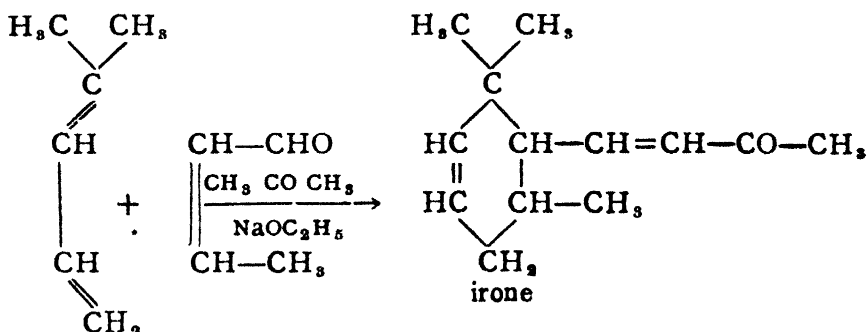
Citral is condensed with acetone in presence of barium hydroxide to yield pseudo-ionone; ($NaOC_2H_5$ in absolute alcohol, gives better yields). The latter, on boiling with sulphuric acid (1%) is changed into a mixture of α and β ionones. The use of BF_3 as the cyclisation reagent greatly improves the yield. Schematically:



Recently cyclisation is effected by the Royal's method. ψ ionone is added to a mixture of H_2SO_4 (95%) and glacial acetic acid (70 : 30), at temperature below 15°C; finally the mixture is poured into

broken ice and ether with rapid stirring. β ionone of 90% purity is obtained.

The isomers are separated from each other by means of sodium bisulphite. They are both liquids: α-isomer b.p. 127° (12 mm.) and the β-isomer b.p. 130 (12 mm.). The additive compound of the α-isomer is less soluble in sodium chloride solution than that of the β-isomer. The ionones possess a violet-like odour and are closely related to *irone* which is the active principle of violet essence. Tiemann and Kruger had assigned to *irone* the following structure based on its synthesis from 1·1, dimethyl butadiene:



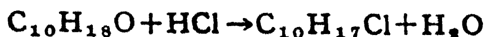
which differs from the structure of the ionones in the position of the double bond. Ruzicka, however, showed that tetrahydroirone is not identical with tetra-hydro-ionone. It has now been conclusively established by Naves and Ruzicka that the natural product irone, is a mixture of several isomers. But the chief constituent is 6-methyl-α ionone called α-irone, the other isomers are 6 methyl-β ionone and 6 methyl-γ ionone. The compound obtained by Tiemann and Kruger from 1·1 dimethyl butadiene and croton aldehyde (see above) is now called γ-ionone.

LINALOOL :—It occurs in the oil of linalo, coriander, bergamot and lavender. It is isomeric with geraniol; on heating with $(CH_3CO)_2O$, linalool is converted into geraniol. This seems to be an *allylic* or *three* carbon system *rearrangement*. This is an example of 'anionono-tropy.'



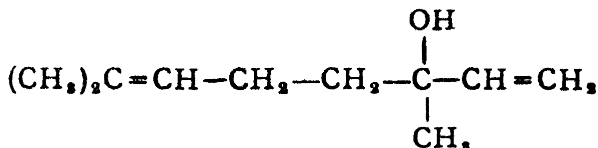
$$R—CH=CH—CH_2OH \longrightarrow R—CHOH—CH=CH_2$$

Linalool is optically active and readily reacts with concentrated hydrochloric acid to give a chloride. The same chloride is obtained from geraniol by the action of HCl.

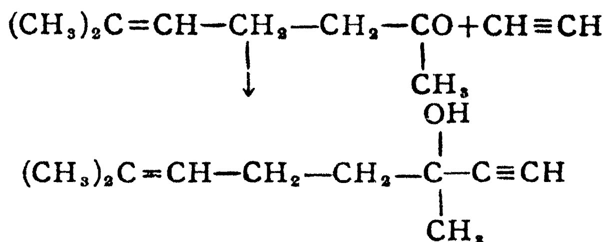


$$C_{10}H_{18}O + HCl \rightarrow C_{10}H_{17}Cl + H_2O$$

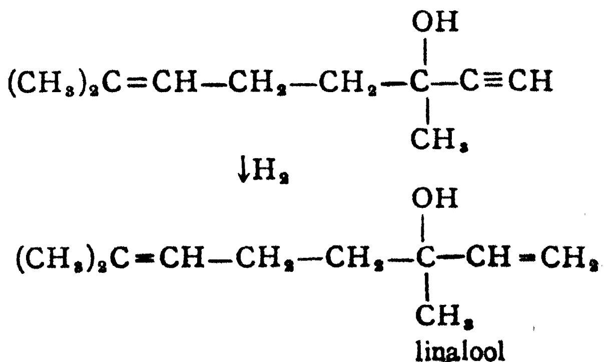
This indicates the presence of a tertiary alcoholic group in the molecule. Hence, it must be a structural isomer of geraniol. It has been assigned the following formula :—



Ruzicka has obtained a complete confirmation of the structure by a synthesis from methyl heptenone. Methyl heptenone is condensed with acetylene in presence of metallic sodium :—

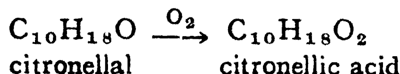


On reduction, by means of moist ether at low temperature, linalool is obtained.

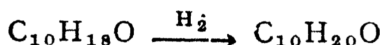


CITRONELLAL :—It is found in the oil of citronella. It is optically active. Its constitution is based on the investigations of Tiemann and Schmidt. Its molecular composition is $C_{10}H_{18}O$.

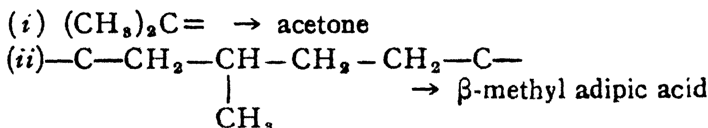
That there is an aldehyde group in the molecule is indicated by (*i*) the oxidation of citronellal to citronellic acid, a monobasic acid, containing the same number of carbon atoms.



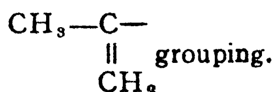
(*ii*) On reduction, citronellal, a primary alcohol, is obtained.



Nature of carbon framework :—This is revealed by the results of oxidation. Tiemann found that oxidation of citronellal in aqueous solution gives acetone and β-methyl adipic acid. Hence, citronellal must contain the following units :—

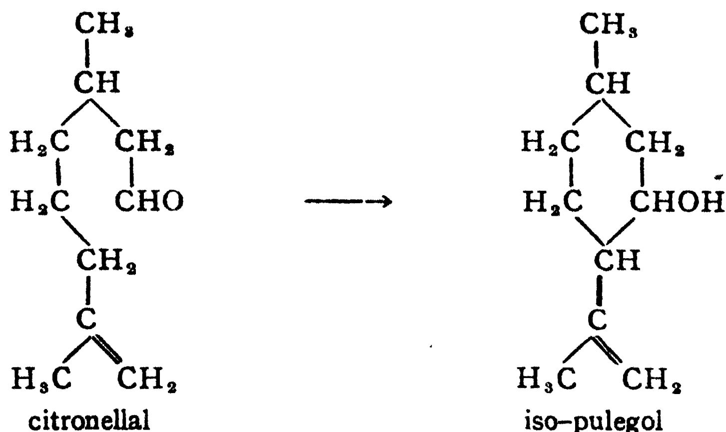


However, when dimethyl acetal of citronellal is oxidised in acetone solution, by means of potassium permanganate, the acetal of dihydroxy-dihydro–citronellal is obtained. On further oxidation with chromic acid, it is changed into a keto-aldehyde. These results indicate the presence of :—

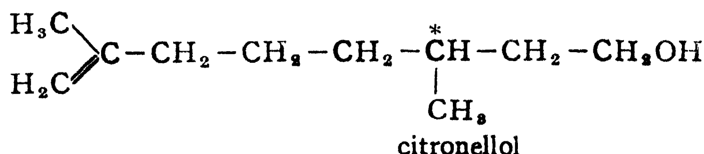


In view of these observations, it may be concluded that under the influence of the oxidising agent in aqueous solution, an isomeric change, involving the shifting of the double bond in the isopropyl group (isopropenyl to isopropylidene) takes place.

The constitution of citronellal is finally settled by its relation to iso-pulegol. On heating with acetic anhydride to 180°, citronellal is converted into iso-pulegol.

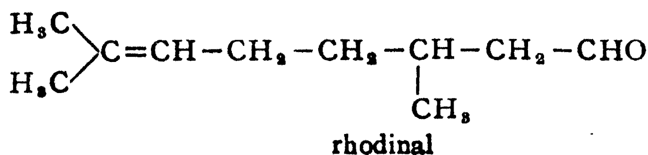


CITRONELLOL:—It is the alcohol corresponding to the aldehyde citronellal, and is obtained from it by reduction with Na and alcohol. It is a constituent of oils of rose and geranium and is closely associated with geraniol. It forms a dibromide derivative, thus indicating the presence of only one double bond. Further, on mild oxidation, it is converted into citronellal. It is optically active and therefore contains an asymmetric carbon atom. Thus, it has the structure :

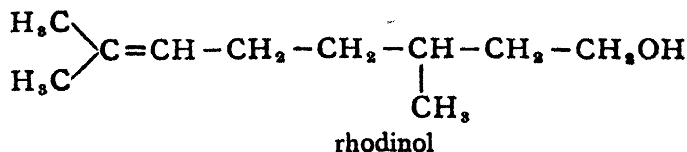


citronellol

RHODINAL and RHODINOL are respectively isomeric with *citronellal* and *citronellol*. They differ in the position of the double bond. Thus, we have :—

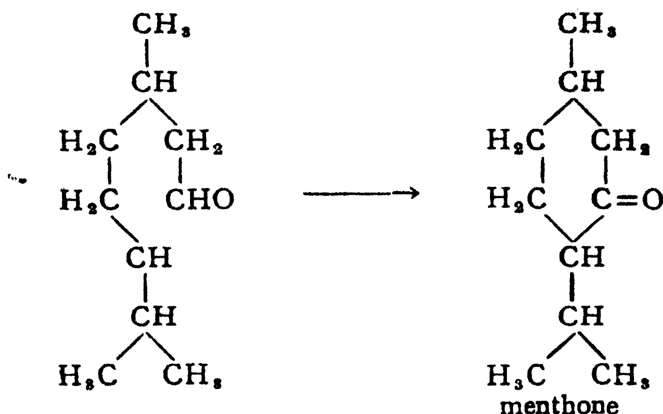


rhodinal



rhodinol

Rhodinal, on heating with acetic anhydride, is converted into menthone.



INTER-RELATIONSHIPS—The inter-relationships existing between the different types of terpenes *i.e.* monocyclic, dicyclic the olefinic and their relation to *p*-menthane can be tabulated as follows:

$(CH_3)_2C=CH—CH_2—CH_2—CO—CH_3$
methyl heptenone

↓ $Zn + ICH_2\text{-}COOC_2H_5$ and dehydration

$(CH_3)_2C=CH—CH_2—CH_2—C(CH_3)=CH—COOH$
geranic acid

↓ (geranic acid → citral)

$(CH_3)_2C=CH—CH_2—CH_2—C(CH_3)=CH—CHO$
citral
↓
geraniol or nerol
↓
linalool

Geranic acid ↓ Na + alcohol

$(CH_3)_2C=CH\text{-}CH_2\text{-}CH_2\text{-}CH(CH_3)\text{-}CH_2\text{-}COOH$
rhodinic acid
↓
rhodinal
↓
rhodinal→citronellol

citral ↘ *p*-cymene

α-pinene ↗ *p*-cymene

α-pinene ⟶ dipentene

α-pinene ↓ camphor ↓ *p*-cymene

α-pinene ↘ terpineol

dipentene ↑ *p*-cymene

dipentene ↓ terpineol → carvone

dipentene ↘ *p*-menthane

p-cymene ↘ *p*-menthane

menthone → menthol → *p*-menthane

Sesqui-terpenes

Sesqui-terpenes are found widely distributed in many essential oils. They possess the general formula $C_{15}H_{24}$, $C_{15}H_{36}$ or the corresponding oxygenated formula $C_{15}H_{24}O$ or $C_{15}H_{36}O$. Ruzicka, following the suggestions from Wallach, has formulated that the sesqui-terpenes, like the mono-terpenes are built up of isoprene molecules by way of simple polymerisation. Thus, three molecules of isoprene may polymerise to give :

(a) a *mono*-cyclic tri-olefinic system, or
(b) a *di*-cyclic di-olefinic system, or
(c) an *open*-chain tetra-olefinic system.

It is interesting to recall that the mono-terpenes which have been discussed, are derived from two isoprene units and fall into the same sub-divisions. Further, as in the case of mono-terpenes there are two fundamental series—*para*-menthane series and *meta*-menthane series. Thus, the sesqui-terpenes exist in two fundamental series—*cadalene and eudalene* series. Our knowledge of this class of terpenes is based largely on the researches of Ruzicka. A large number of reactions have been explored in his systematic investigation. Some of the typical and important ones are :—

(a) addition reactions with halogen acids, halogens etc.
(b) ozonolysis,
(c) graded oxidation and
(d) dehydrogenation (Vesterberg).

The last reaction *viz.* dehydrogenation, which is effected by means of sulphur or selenium, has been of immense help in the elucidation of the structure of the sesqui-terpenes. A high temperatures, many of the natural sesqui-terpenes are converted into naphthalene derivatives which can be readily identified. In addition to the above chemical methods, purely physical methods, e.g., the study of molecular refraction, parachor etc. have been employed for the structural elucidation of these terpenes. The values of molecular refraction for the different systems are calculated to be as under :—

Monocyclic.	3 double bonds	67.8	Mol Ref.
Di-cyclic	2 „ „	66.1	„
Tri-cyclic	1 double bond	64.4	„
A-cyclic	4 double bonds	69 5	„

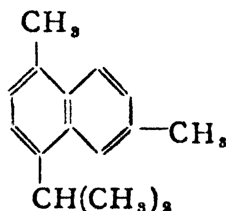
A knowledge of the value in the case of a natural terpene can be used to indicate the probable structure of the compound.

MONOCYCLIC SESQUI-TERPENES :—The important members of this group are *zingiberene* and *bisabolene*. *Zingiberene* is found in the oil of ginger. It possesses the molecular composition $C_{15}H_{24}$. It is optically active. Its constitution has been established as follows :

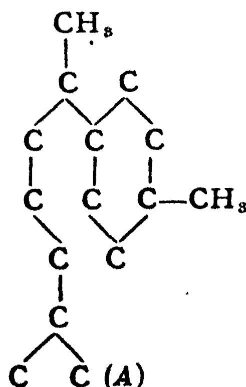
(1) *Nature and amount of unsaturation* :—*Zingiberene* in presence of platinum black can be reduced to hexa-hydro zingiberene $C_{15}H_{30}$. This indicates that zingiberene is a monocyclic sesquiterpene with three double bonds. Further, the observed value for the molecular refraction for zingiberene is higher than the one calculated on the basis of three isolated double bonds. Now, it is a well-known fact that conjugation tends to raise the refractivity of a molecule above its normal value. Hence, zingiberene must contain at least one conjugated system of double bonds. This is confirmed by the fact that Na and alcohol reduces zingiberene to dihydrozingiberene.

(2) *Nature of carbon framework* :—This is reavealed by the results of (*a*) dehydrogenation with sulphur and (*b*) of ozonolysis.

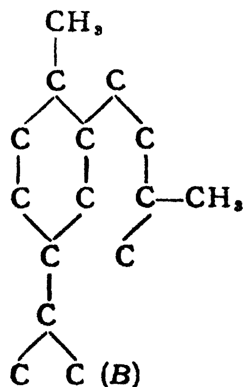
When heated with sulphur, zingiberene is changed into *cadalene* $C_{15}H_{18}$. The latter has been obtained synthetically and its structure proved to be 1,6-dimethyl-4-isopropyl naphthalene :—



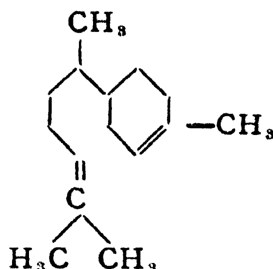
Hence, zingiberene must contain the cadalene skeleton.



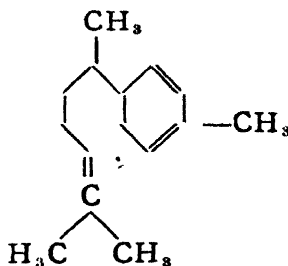
or



Ozonolysis of zingiberene gives acetone, levulinic acid and succinic acid. Further, dihydrozingiberene on oxidation with $KMnO_4$ gives a keto-dicarboxylic acid which with NaOBr gives a tricarboxylic acid. This indicates a CH_3-CO group in the ketodicarboxylic acid. These results the position of two of the three double bonds as follows :



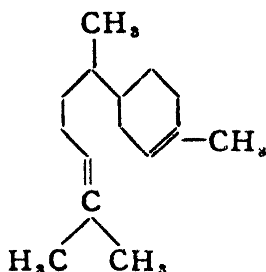
the position of the third double bond which is in conjugation with either of the double bonds in the above formula is indicated by the formation of an adduct with methyl acetylene dicarboxylate which on heating gives 2.6 dimethyl octa-2, 7 diene and methyl 4 methyl phthalate. Thus we have the structure :



which satisfactorily accounts for the adduct with methyl acetylene dicarboxylate and its products of pyrolysis.

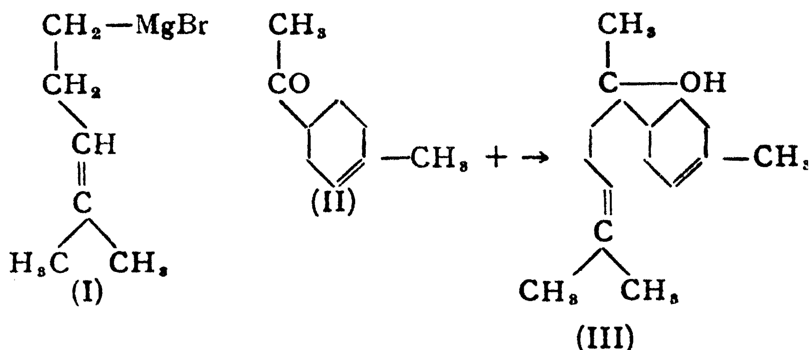
Bisabolene : It is found in the oils of lemons and pine. It is isomeric with zingibrene. By Vesterberg'smethod, it gives cadalene; on ozonolysis, it gives acetone and levulinic acid. Bisabolene adds on three molecules of HCl to form bisabolene tri-hydrochloride. Hence bisabolene contains *three* double bonds and one ring. Further

there is no conjugated system of double bonds. Bisabolene is also formed from nerolidol. The structure proposed is :—

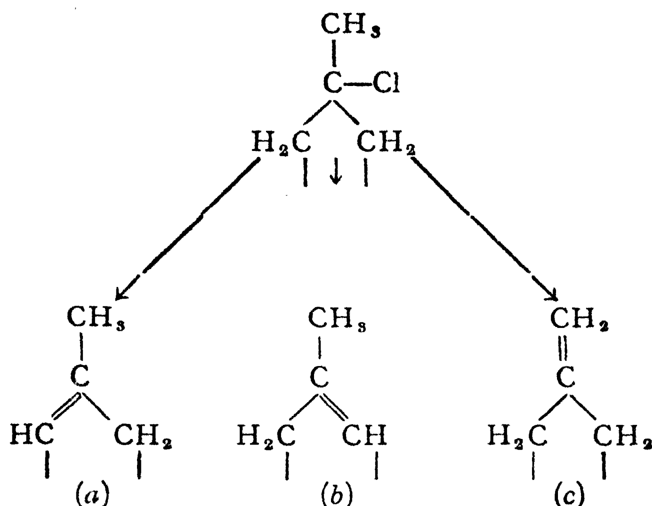


This is in agreement with the isoprene rule (Three units linked head to tail.)

A complete synthesis of bisabolene has been achieved. It consists in the condensation of 2-methyl-pentenyl-2 magnesium bromide (I), with 1-methyl-4-acetyl cyclo-hexene (II) to form the alcohol, *bisabol* (III).



The tri-hydrochloride of (III) is identical with the tri-hydrochloride of bisabolene. The hydrochloride when heated with acetic acid and sodium acetate, gives a monocyclic sesqui-terpene which resembles very closely the natural bisabolene, but is not identical with it. This is because hydrogen chloride may be eliminated from the molecule in three different ways and hence, the product is a mixture of all the three isomers :



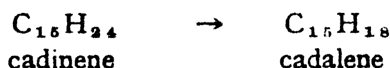
the elimination as according to (b) leads to the structure proposed.

DICYCLIC SESQUI-TERPENES :—The most important member of this series is *cadinene.* It occurs in the oil of cubebs.

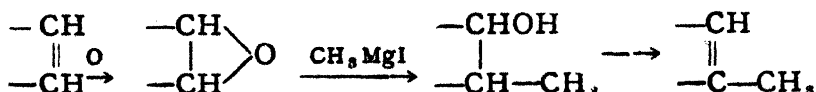
CONSTITUTION :—Its molecular composition is $C_{15}H_{24}$.

Degree of unsaturation :—On catalytic hydrogenation, it gives tetra hydro cadinene, which indicates that it is a dicyclic sesquiterpene with only two double bonds; there is no exaltation of the molecular refractivity. Hence the double bonds are not conjugated.

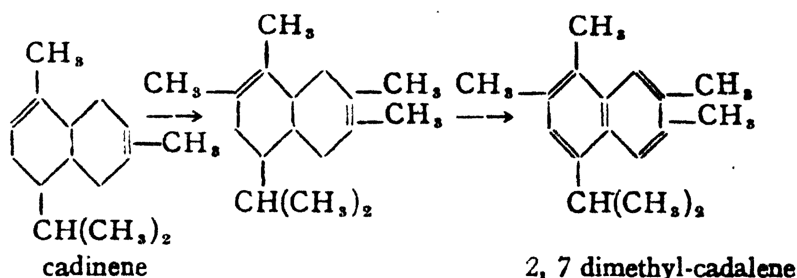
Carbon skeleton :—When heated with sulphur, it is converted into cadalene :



Hence it follows that cadinene must contain the cadalene structural unit. It also contains two double bonds. The exact position of the double bonds is established as follows :—Cadinene is first converted into the mono-and di-epoxides, by the action of perbenzoic acid. The epoxides are then treated with CH_3MgI and subsequently dehydrated to yield mono and dimethyl cadinenes. These reactions help to fix the positions of the epoxide ring and hence that of the double bond. This is the method developed by Ruzicka and Sternbach for locating a double bond in a terpene molecule. Schematically :



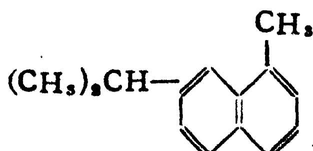
The dimethyl cadinene obtained in this way, on dehydrogenation, gave 1, 2, 6, 7 tetramethyl-4-iso-propyl-naphthalene *i. e.* 2, 7 dimethyl cadalene. Hence the double bonds are in positions 1, 2 and 6, 7.



This is further confirmed by the results of ozonolysis : on ozonolysis, cadinene gives a compound containing the same number of carbons as cadenene. Hence they must be in two different rings and not in the same ring.

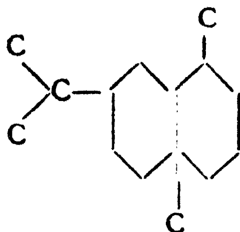
CADINOL :—It is the sesqui-terpene alcohol closely related to cadinene. On dehydration, it is converted into cadinene and hence, it should contain the cadalene skeleton. The alcoholic group appears to be a tertiary one as indicated by the failure of cadinol to react with phthalic anhydride. At present, cadinol is supposed to be a mixture of a number of structural isomers, which are hydroxy cadinenes.

SELINENES :—The mono and dicyclic terpenes, hitherto discussed, are related to and derived from the cadalene skeleton. In addition a few dicyclic sesqui-terpenes are known which are called *selinenes*, and which contain the *eudalene* unit :

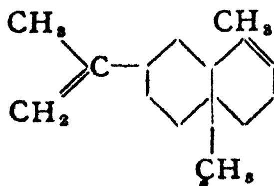


The cadalene and eudalene units are related to each other as the para and meta menthanes.

SELINENE which is found in oil of celery is a representative of this class. On heating with sulphur, it readily gives eudalene which is proved to be 1-methyl-7-isopropyl naphthalene. There is also the loss of a CH_3 group as methyl mercaptan, which indicates that there must be an angular methyl group. The position of the latter is inferred on the basis of the isoprene rule. The structural skeleton for selinene is :—



α-Selinene gives on catalytic hydrogenation tetra hydro selinene $C_{15}H_{28}$. Hence it contains two double bonds and two rings. The position of the double bonds is established by the results of ozonolysis. α-Selinene on ozonolysis gives a dike-to-mono carboxylic acid whi-h with NaOBr gives tri-carboxylic acid. This indicates the existence of two CH_3CO groups in the product of ozonolysis. Hence the double bonds are placed as in



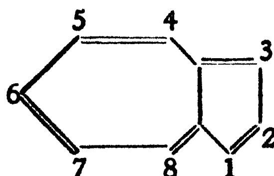
Azulenes : The essential oils : oil of geranium, oil of chamomile, oil of guianol and oil of vetiver, contain blue—violet components which are extracted by shaking their ethereal solution with H_3PO_4. They possess the following characteristics.

(1) The molecular composition is $C_{15}H_{18}$

(2) They form complexes with 1, 3, 5 trinitro benzene.

(3) on hydrogenation, they yield decahydro derivatives which indicates the presence of five double bonds and two rings in the molecule. The values of molecular refraction also confirm the same.

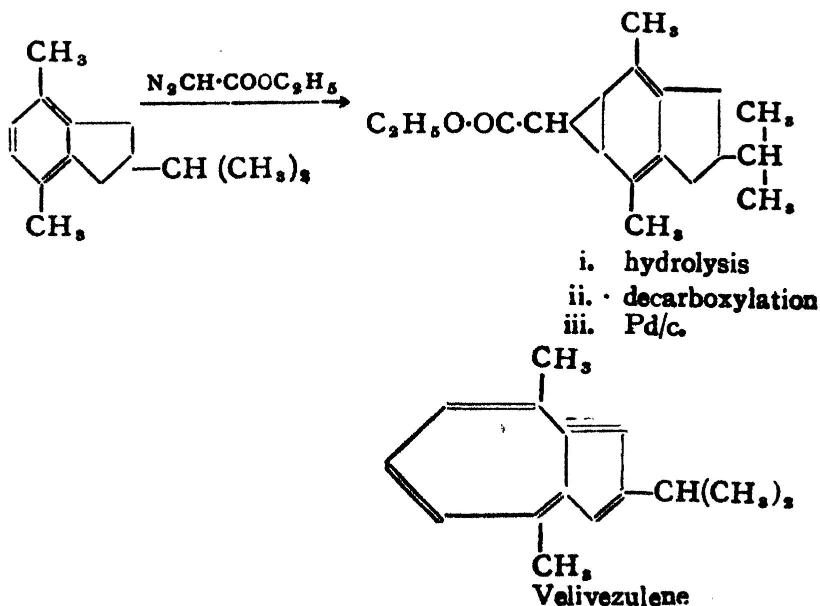
Plattner was the first to suggest that the dicyclic system present in them is the azulene system, built up of a seven-membered ring and a five-membered ring.



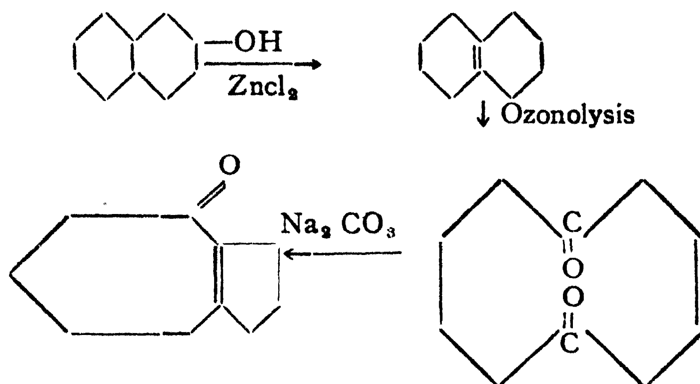
azulene is thus isomeric with naphthalene but forms blue-violet crystals which melt at 99°.

The natural oils e.g. oil of chamomile etc. are sesqui-terpenes with the molecular compositions $C_{15}H_{24}$ and are converted into the azulenes on dehydrogenation with S or Se. Thus the oil from guiaol, is *guiacazulene* is rich 1·4 dimethyl isopropyl azulene; the oils of chamomile and vetive are found to be 1·5, dimethyl-8 isopropyl azulene and 4-8, dimethyl-2 isopropyl azulene respectively.

Synthetic methods have been developed for obtaining the azulenes.—Vetivazulene has been synthesised as follows :—

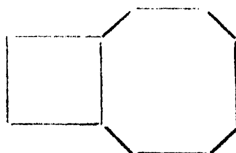


Azulene itself is obtained from β- decanol.



Reduction of the keto derivative with amalgamated Zinc and HCl and subsequent dehydrogenation with Pd|C gives azulene.

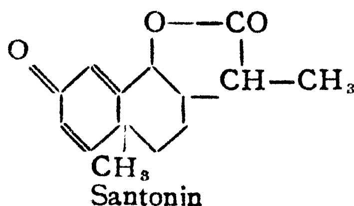
Caryophyllenes : They are constituents of the oil of cloves. They possess the molecular formula $C_{15}H_{24}$ and are classified as sesquiterpenes; on catalytic hydrogenation, they form a tetrahydro derivative $C_{15}H_{28}$ thus indicating the presence of two double bonds and two rings in the molecule. The C_{15} system is built-up of three isoprene units linked head to tail. Further it has been now shown that they contain a dicyclic system built up of a four-membered ring and nine-membered ring.



The presence of the four-membered ring was indicated by the formation of dimethyl-cyclobutane-dicarboxylic acid on oxidative degradation; the presence of a nine-membered ring was deduced by Barton as a result of extensive degradative studies. The structural investigations bristled with many difficulties as the caryophallene molecule readily undergoes isomerisation and cyclisation.

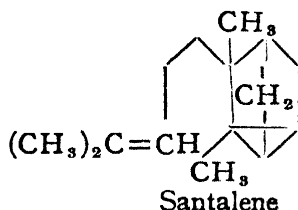
Santonin : It is the chief constituent and active principle of worm seed. Its composition is $C_{15}H_{18}O_3$. It is found to be an oxygenated derivative of a dicyclic sesquiterpene containing the eudalene system.

It is also a lactone. Clemo and Haworth has assigned the following structure to it.



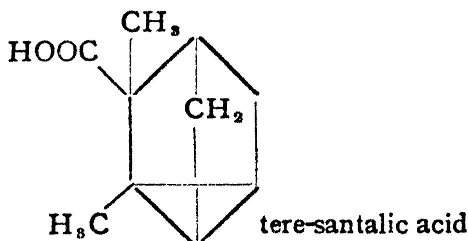
Santonin

α—Santalene : This is a member of the tricyclic sesquiterpenes, It is found in the oil of Indian Sandalwood. It is an eudalene derivative and has been assigned the formula :



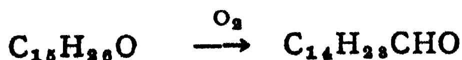
Santalene

It is based on the study of the decomposition products on oxidation. α-Santalene is gradually decomposed, according to Semmler, into tere-santalic acid



OPEN-CHAIN SESQUI-TERPENES :—The most important members of this class are *farnesol nerolidol.* They are much used in perfumery.

FARNESOL is a constituent of many oils, *e. g.* oils of lime flowers, oils of lillies of the valley, oil musk etc. Its composition is $C_{15}H_{26}O$ On oxidation. it forms an aldehyde.



$$C_{15}H_{26}O \xrightarrow{O_2} C_{14}H_{23}CHO$$

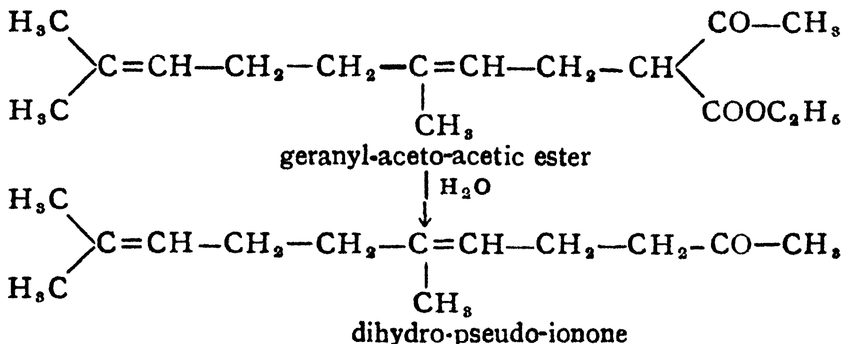
This indicates the presence of a primary alcoholic group.

The oxime of the aldehyde, $C_{14}H_{23}CH{=}NOH$, on dehydration gives the nitrile.



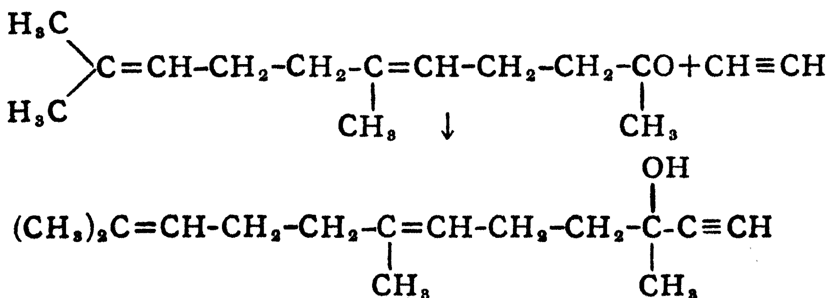
$$C_{14}H_{23}CH{=}NOH \rightarrow C_{14}H_{23}.CN + H_2O$$

The nitrile, on hydrolysis, gives :— (*a*) the corresponding acid, $C_{14}H_{23}.\ COOH$ and (*b*) a ketone $C_{13}H_{23}O$ which is identified as dihydro-pseudo-ionone. The latter has been synthesised by the ketonic hydrolysis of geranyl-aceto acetic ester.

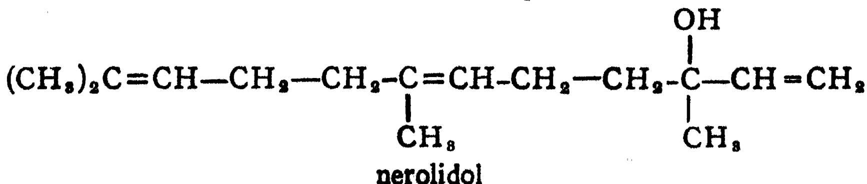


Thus, dihydro-pseudo-ionone has the composition $C_{13}H_{22}O$ which is less than that of farnesol by two carbon atoms.

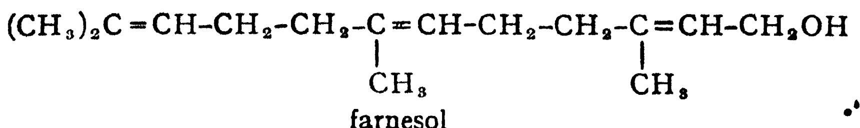
Farnesol is synthesised by condensing dihydro-pseudoionone with acetylene in presence of metallic sodium, or $NaNH_2$.



which on reduction with moist ether, gives the isomeric nerolidol.



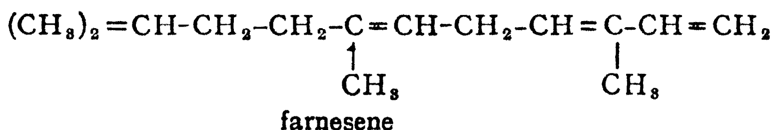
On heating with acetic anhydride, isomerisation takes place and farnesol is obtained.



farnesol

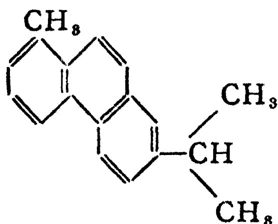
Farnesol or nerolidol, under the influence of concentrated acid is converted into bisabolene.

FARNESOL :—$C_{15}H_{24}$ is obtained by the dehydration of farnesol and has the structure :—



farnesene

HIGHER TERPENES :—So far we have discussed some of the mono-terpenes and sesqui-terpenes. The former are derived from benzene and the latter, from naphthalene. In addition to these, many di-and tri-terpenes are known, which are closely related to phenanthrene. Abietic acid, the chief constituent of rosin—the residue left after the distillation of turpentine, is a di-terpene carboxylic acid. On dehydrogenation with sulphur, retene, 1-methyl 7-isopropyl phenanthrene is formed :—



The vegetable resins and balsams constitute chiefly the complex di-terpenes of which very little is known at present. The saponins or sapogenins are closely related to the still more complex tri-terpenes. Rubber represents the most complex of all the poly terpenes.

RUBBER

INTRODUCTION :—The source of all natural rubber is the 'latex', the milky liquid exudation from some tropical trees of Apocynaceæ,

Euphorbiaceæ and Moraceæ families. The best rubber or caoutchouc (wood tears) is obtained from the tree Hevea, indigenous to Brazil. The latex is an emulsoid and holds the rubber hydrocarbons in solution; the crude latex contains about 90-95% of the rubber hydrocarbon; coagulation by heat precipitates the rubber which constitutes the crude rubber of commerce. A nnmber of methods have been developed for the separation of rubber from the latex. In some cases, the latex is stabilised by the addition of ammonia and in this form it constitutes an important article of commerce.

General Properties and Composition:—Rubber is a highly complex mixture. It is a colloid, soluble in benzene, chloroform, carbon disulphide, carbon tetrachloride and ligronin. It is unsaturated and combines with chlorine, oxygen, ozone and nitrogen oxides (N_2O_3). A nitrosite of the composition $(C_{10}H_{15}N_3O_7)_2$, is formed, when nitrous oxides are passed into a benzene solution of rubber. It is a yellow powder soluble in ethyl acetate and acetone; it decomposes at 158-160°. This reaction is the basis of a technical method for the quantitative estimation of rubber in rubber goods. When heated with sulphur or with sulphur mono-chloride (S_2Cl_2). in carbon disulphide, it becomes vulcanised; the process results in the formation of a product which retains its elastic properties over a wider range of temperature than the raw rubber and also increases its resistance to chemical reagents. The process of vulcanisation is accelerated by the use of small quantities of sulphur containing organic compounds, called "accelerators"; one of the most important is *thio-carbanilide.* It is probable that vulcanised rubber contains sulphur held in chemical combination with part of the rubber. A greater proportion of sulphur yields a product known as '*ebonite*' or '*vulcanite*'. It is harder than vulcanised rubber.

Chemical Constitution:—The empirical composition of natural rubber is given by the formula (C_5H_8). It is a highly complex compound with no melting or boiling-point. Its molecular weight is still unknown. The modern methods used for the determination of the molecular weights of macromolecules, and which involve osmotic pressure, viscosity and ultra centrifuge studies, all give for the molecular weight values which range between 180,000 and 400,000. These results indicate that the rubber is built up of giant molecules. Hence the molecular formula for rubber may be

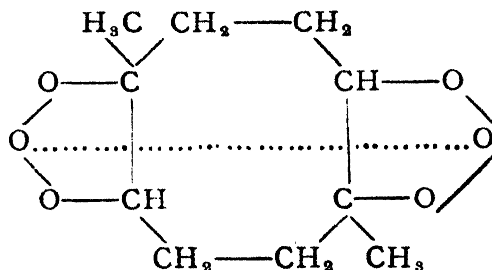
expressed as $(C_5H_8)n$. This formula has, however, one great advantage that it indicates a close relationship to isoprene.

THE NATURE OF THE PROBABLE STRUCTURAL UNIT —Our knowledge of the constitution of rubber is due chiefly to the researches of Tilden, Harries and Staudinger and is based on:—(*a*) the formation of additive compounds with bromine. ozone, and nitrogen oxides, (*b*) the nature of the decomposition products of ozonides *i. e.* results of ozonolysis and (c) its relation to isoprene. However, despite a large amount of research work, the problem of the constitution of rubber remains still unsolved. So far it has been possible to know only the probable unit out of which the com·plex rubber molecule has been built up.

(*a*) Rubber forms with ozone, an ozonide of the composition $C_{10}H_{16}\ 2O_3$ (Harries). When this ozonide was decomposed with water, Harries isolated the following compounds :—

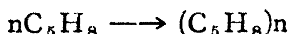
(*i*) levulinic aldehyde; (*ii*) levulinic acid: (*iii*) levulinic peroxide. The products (*ii*) and (*iii*) are probably secondary, the primary products, of ozonolysis being the aldehyde.

Harries in order to account for the formation of these decomposition products, has suggested that the ozonide from rubber which has the composition $C_{10}H_{16}.2O_3$ be formulated as :—



The decomposition of the ozonide by the usual catalytic hydrogenation, is supposed to occur along the dotted line. Such a decomposition would yield two molecules of levulinic aldehyde. $CH_3—CO—CH_2—CH_2—CHO$. An inspection of the above formula for the ozonide, further reveals that it is made up of two isoprene units joined together in the 1.4 addition way. These result of ozonolysis, therefore, indicate that the ultimate unit of the rubber molecule is the isoprene unit.

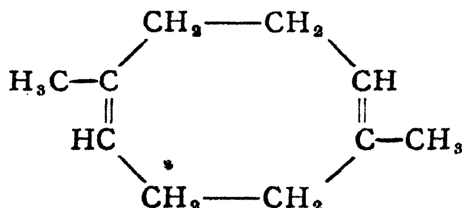
(*b*) When rubber is distilled destructively, a complex mixture of isoprene, dipentene and hevene is formed. The last two hydrocarbons are closely related to isoprene as they represent its simple condensation products. These results show that rubber contains actual or potential isoprene molecules. These conclusions, arrived at from the analytical evidence, are further corroborated by the results of synthesis. Tilden, in 1892, had announced that isoprene, on standing, is converted into a rubber-like product.



$$nC_5H_8 \longrightarrow (C_5H_8)n$$

Later on, Hofmann changed isoprene into rubber by the action of heat. Another synthesis is due to Mathews and Harries. Both of them independently discovered that isoprene is polymerised in the presence of metallic sodium to a rubber-like product. Thus, the view that the *structural unit* of the rubber molecule is the *isoprene unit*, stands well established. The next problem is to decide the *number* and the *mode of linking* of these isoprene units in the complex rubber molecule. Various theories have been formulated regarding the size and the structure of the rubber complex. The exact number of the isoprene units contained in the molecule remains still unknown, as the molecular weight of rubber has not yet been determined with scientific precision. It is now generally accepted that the rubber molecule is a polymer of simple isoprene.

Harries first suggested that a *closed eight carbon ring* system is the basis of the rubber molecule. This suggestion rested on the results of ozonolysis of rubber. He had isolated an ozonide $C_{10}H_{16}2O_3$ which was obviously the ozonide of a cyclo-octadiene. Two isoprene units are united in the 1·4 addition way, to form a closed chain compound, 2–6 dimethyl Δ 1–5 cyclo-octadiene.

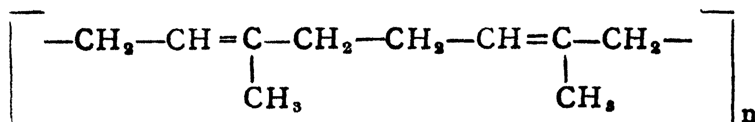


The above cyclo-octadiene molecule then undergoes polymerisation to yield the complex rubber.

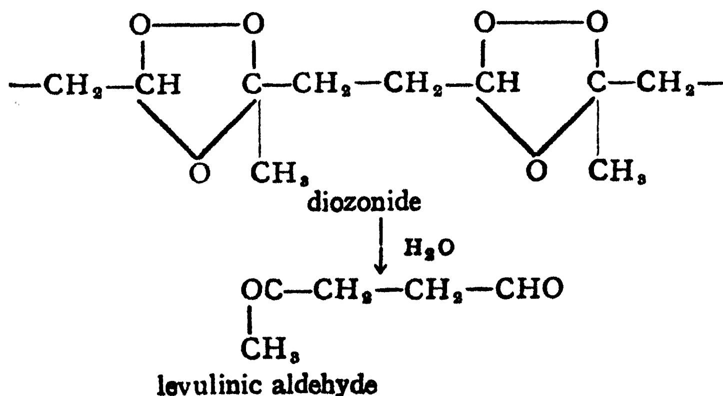
Such a view, however, has some limitations. If the rubber molecule is a polymer of this cyclo-octadiene system, the poly-

merisation would involve the disappearance of some of the double bonds. This would preclude the formation of the ozonide, which however, has been actually obtained. Harries met this difficulty by proposing that the polymerisation of the eight-membered ring was a kind of loose addition by means of Thiele's partial valencies, and that the rubber molecule is depolymerised by ozone and hence, gives the diozonide. But there is no reason to suppose why ozone alone and not any other reagent should have a depolymerising effect. Bromine gives a bromo-derivative which is as complex as rubber itself; similarly, the compositions of the nitrosites are very complicated. Secondly, there is no experimental evidence for the formation of such eight-carbon systems when rubber is decomposed. Lastly, the known octadienes polymerise to give crystalline products entirely different from rubber.

Pickles has proposed an open-chain structure with head to tail linking of the isoprene units, for the basic unit: it is a case of linear polymerisation (isoprene units linked head to tail.



Such a formulation readily accounts for: (*i*) the formation of a diozonide, (*ii*) the results of ozonolysis, (*iii*) the addition products of rubber with Br_2, H_2 and HCl, in which one mole of each of these reagents is added for each five C atoms in the molecule.



The complex rubber molecule is supposed to have been built up of the above units repeated a number of times. Such a re-

presentation also accounts for the observed unsaturation of the complex rubber molecule. A similar view has been advanced by Staudinger. He obtained, by hydrogenation of rubber with molecular hydrogen, in the presence of platinum at 270°, hydro-carbon with the empirical composition (C_5H_{10}). The product is a saturated compound and unlike raw rubber, it is not attacked by bromine or nitrogen oxides. On dry distillation, it yields β-methyl butene. The latter, on oxidation gives $CH_3—CH_2—CO—CH_3$. These relations can be interpreted readily on the basis of the presence of a basic unit with open-chain structure :—

$$—CH_2—CH=\underset{\substack{|\\CH_3}}{C}—CH_2 \vdots —CH_2—CH=\underset{\substack{|\\CH_3}}{C}—CH_2 \vdots —CH_2—CH=$$

$$\downarrow H_2$$

$$-CH_2-CH_2-\underset{\substack{|\\CH_3}}{CH}-CH_2 \vdots -CH_2-CH_2-\underset{\substack{|\\CH_3}}{CH}-CH_2 \vdots -CH_2-CH_2-$$

$$\downarrow \text{pyrolysis}$$

$$CH_3—CH_2—\underset{\substack{|\\CH_3}}{C}=CH_2 + CH_3—CH_2—\underset{\substack{|\\CH_3}}{C}=CH_2$$

$$\downarrow O_2$$

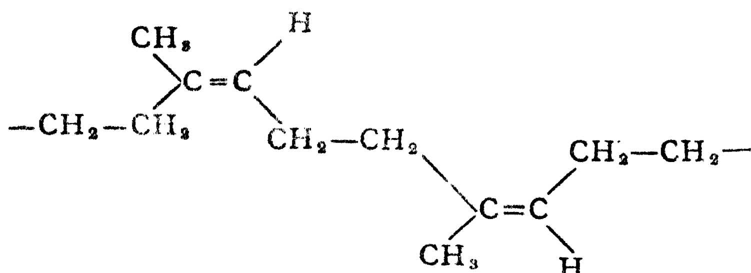
$$CH_3—CH_2—\underset{\substack{|\\CH_3}}{C}=O + CH_3—CH_2—\underset{\substack{|\\CH_3}}{C}=O$$

methyl-ethyl-ketone methyl-ethyl-ketone

It must be however mentioned that Pummerer and Bouchards obtained on hydrogenation (Pt. + H_2 at 80°) of rubber in hexahydro-toluene solution, a product different from that obtained by Staudinger. Finally, there is the question of the nature of the end-groups or the extent of cross linkages of chains; the formation of a small quantity of succinic acid, formic acid and CO_2 may arise from the end-groups. As rubber is thermo plastic and becomes soft on heating, there is little if any, cross-linkage of chain in the rubber molecule.

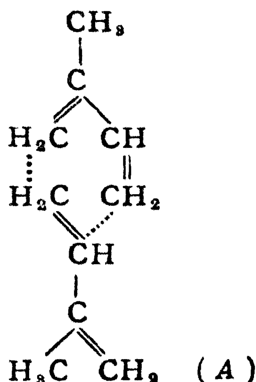
Recently, a synthetic rubber resembling very closely natural rubber has been obtained by polymerising isoprene with Ziegler catalyst, $[TiCl_3\ Al(C_2H_5)_3]$. It is a polyisoprene of cis 1·4 configuration. It is called Ameripol SN. Firestone has developed the Coral rubber indistinguishable from the natural one, by polymerising isoprene with Li metal.

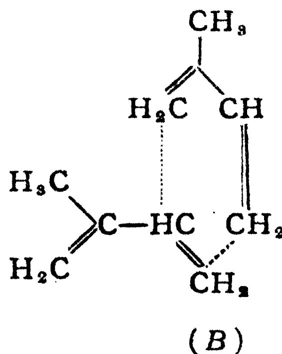
Recently some independent physical evidence based on X-ray analysis has been obtained. Katza and later on, Meyer as a result of the examination of the stretched films of rubber, have shown that the distance between repeating units in the fibre axis correspond to two isoprene units. The CH_3—groups thus occupy *cis* positions with regard to the double bonds.



Gutta-percha which resembles rubber very closely is also built up of isoprene units like rubber. The difference however is in the arrangement of the—CH_3—groups with regard to the double bonds. In gutta-percha, they possess a *trans* configuration as opposed to the *cis* in the ordinary rubber.

FORMATION OF TERPENES IN NATURE :—All terpenes, mono-terpenes, sesqui-terpenes, whether monocyclic, dicyclic or openchain are found to contain a structure which is made up of a definite number of isoprene units. In the case of the mono-terpenes, two molecules of isoprene are united in such a way that some of the following systems are found. The *p*-menthane system (*A*), *m*-menthane system (*B*), the *di*-cyclic system (*C*) and the openchain system (*D*).





CHAPTER V

ALKALOIDS

INTRODUCTION :—Alkaloids comprise an important group of natural nitrogenous organic compounds of vegetable origin with *pharmacological and physiological properties.* They constitute the '*active principles*' of the common vegetable drugs. They are *basic, complex nitrogenous* compounds and hence, their class-name "alkaloids," which means (alkali-like). They occur fairly widely in nature in many plants. The most common plants which contain them in large amounts are di-cotyledons ; the following families are the typical ones :—

poppies, opium	papaverine, morphine
cinchona	quinine, cinchonine
deadly night-shade, datura henbane ..	atropine, hyoscyamine
coca	cocaine, ecgonine
lupins	lupinine

The alkaloids are localised in certain parts of the plants, *e.g.*, seeds, roots, bark and leaves. They are not present in the free state, but occur as salts of the usual plant acids like malic, cirtic, oxalic and tartaric acids, and rarely in combination with characteristic acids *e.g.* meconic and quinic acids. Usually, more than one alkaloid are contained in the plant material. Further, these alkaloids, which are associated in this way are closely related in structure. The alkaloidal content of a plant depends on many factors. It is influenced by the nature of cultivation—the place and time ; the quinine content of the cinchona cultivation in Java has, thus, been greatly increased by varying the mode of cultivation. Recently, colchicine has been isolated from meadow saffron—a monocotyledon. It is used in biological experimentation ; it causes the doubling of the chromosomes in some plants. Here is a possible method of producing a new species. It is also used in the treatment of gout and for the relieving of inflammation.

The exact functions of the alkaloids in the plants are not known. They are the products of metabolism; or they may be the reserve material stored for protein synthesis; or they serve as protective substances to ward off animal or insect attack; they may also function as plant stimulants or regulators similar to the hormones. They are usually concentrated in the living tissue at points of intense cell activity, whence they are transferred and stored in such dead structures as the seeds, hulls or the bark.

GENERAL COMPOSITION AND BEHAVIOUR:—Most of the alkaloids contain *C,H,O* and *N*. At least some of the *N* forms part of a reduced hetero-cyclic system. The principal systems are pyrrole, pyridine, quinoline, iso-quinoline and tropane. There is also the non-nitrogenous phenanthrene system, which is present in the morphine group of alkaloids. A few alkaloids are known which are simple derivatives of phenyl-alkylamines; the typical ones are hordenine and ephedrine.

Alkaloids are usually crystalline and non-volatile solids. Members of the coniine and nicotine group contain only *C*, *H* and *N* and are volatile liquids. Majority of them are *tertiary* bases; they react with methyl iodide to give crystalline addition products. A few of them are secondary bases like coniine; in a few others, the nitrogen is present as the acid amide function, *e.g.* in piperine. Many are present as methyl ethers; the methylene-ether linking also occurs frequently. Probably, formaldehyde is the methylating agent. Nearly all of them are optically active and laevo-rotatory. Papaverine is optically inactive. Coniine is dextro-rotatory. They are insoluble in water, but soluble in alcohol, ether and chloroform. With inorganic and organic acids, *e.g.* sulphuric acid, halogen acids, salicylic acid, they form soluble crystalline salts; the chlorides and sulphates are very common. Almost all possess characteristic physiological action and are very poisonous. But in regulated quantities, they are employed with great benefit to the human system. Thus, strychnine is a very important general stimulant, quinine is still the useful anti-malarial, cocaine finds extensive applications as a local anæsthetic. Morphine is used as a soporific and to relieve all kinds of physical pain. Atropine is a typical mydriatic alkaloid, employed in causing the dilatation of the pupil of the eye.

ISOLATION OF ALKALOIDS :—There are two important methods which are commonly used for the extraction of alkaloids from the natural sources. The principle of one of the methods, is that a soluble salt of the alkaloid is first prepared which is then extracted. The vegetable matter, finely divided or cut, is treated with dilute acids like hydrochloric, sulphuric or acetic acid. This treatment converts the alkaloids into a soluble salt which is then isolated. Or in a slightly modified process, the finely divided plant material is repeatedly extracted with alcohol; the alcohol is then removed under reduced pressure and the residue taken up with organic acids when the alkaloidal matter present is extracted as the soluble salts. The free alkaloid is liberated from the salt by the action of a mild alkali like sodium carbonate or ammonia and subsequently obtained by one of the following operations :—(*a*) filtration, if insoluble, (*b*) extraction with solvents like alcohol, ether or chloroform, and (*c*) steam distillation, if volatile. The crude alkaloids obtained by one of these methods are further purified by recrystallisation of the free compounds or their salts. The commonly employed salts are the hydrochlorides, sulphates and oxalates, which crystallise very well.

In the other method, the alkaloid is liberated from the natural raw material and is then extracted with a suitable solvent. The vegetable matter is digested with ammonia when the alkaloid is liberated in the free condition. It is then extracted with a solvent like ether, alcohol or chloroform. The solution is subsequently treated with hydrochloric acid gas and the alkaloid is precipitated as its hydrochloride. The neutral compounds associated with it, in the plant, remain in solution in the organic solvent. The separation of the alkaloid is almost quantitative. The individual members are further separated by fractional extraction or by fractional precipitation. Gadamer has developed an elegant method based on the above principle. The mixed alkaloids in dilute acid solutions are treated with small quantities of ammonia; the least basic alkaloid is, thus, precipitated first and is extracted with a suitable solvent. The last fractions contain the most basic compounds. Or conversely, the mixture of alkaloids is dissolved in C_6H_6, $CHCl_3$ and the solution repeatedly extracted with small amounts of an acid; the strongest bases are extracted first.

Recently an entirely new technique based on the ion exchange principles has been developed for the isolation of the alkaloids. The alkaloids which form a positive ion, with H^+ ion, are absorbed smoothly, on an hydrogen ion exchanger. They are then removed from the exchanger by regeneration with alkali together with a suitable solvent like alcohol or acetone.

NOMENCLATURE AND CLASSIFICATION.—So far a systematic classification and nomenclature of alkaloids has not been possible. The names of many alkaloids have been derived from the plants which contain them *e.g.* papaverine and berberine. Some, like morphine and narcotin, get their names from the specific physiological action. Pelletierine has the name of its discoverer. In the case of minor alkaloids which are associated together, the names are derived from that of the principal alkaloid by the addition of prefix or suffix *e.g.* in cinchonine series. The closely related ones are given transposed names; thus we have narcotine, contranine and tarconine, and nicotine continine and ticonine. Prefixes such as *iso*, *pseudo* and *neo* or the Greek letters, are used to designate the transformation and isomeric products.

Henry has proposed a classification which is based on the nature of the hetero-cyclic units, present in the alkaloids. There are nine groups, with a tenth for the alkaloids of unknown constitution :—

ALKALOID	GROUPS
nicotine hygrine	pyrrolidine
conine nicotine piperine	pyridine
quinine strychnine	quinoline
papaverine	iso-quinoline
atropine cocaine	tropane

ALKALOID	GROUPS
harmine	indole
pilo-carpine	glyoxaline
morphine codeine	phenanthrene
hordenine ephedrine	phenyl-alkylamine
aconitine	unknown

(*N.B.*—The phenanthrene unit is a non-nitrogenous, polycyclic unit and in phenyl alkylamine, the nitrogen forms part of an open chain structure).

GENERAL ALKALOIDAL REAGENTS.—The alkaloids as a group react with certain reagents which are called alkaloidal regents. The reactions are characterised as :—(*i*) colour reactions and (*ii*) precipitation reactions.

THE COMMON COLOUR REAGENTS.—These are concentrated sulphuric acid, nitric acid, potassium dichromate, potassium permanganate and molybdic acid. These reactions are often used for the detection and identification of small quantities of the alkaloid. The colour produced on moistening the residue obtained by evaporation of a solution, supposed to contain the alkaloid, is compared with that from a sample of a known alkaloid. Some of these reactions are very sensitive and characteristic of the alkaloid.

THE PRECIPITATING REAGENTS.—These reagents readily combine with alkaloids to give precipitates which can be used in conjunction with the colour reactions for the detection and identification of alkaloids. The precipitates possess in some cases, a definite composition and a characteristic crystalline form and hence, can be used for the identification of the alkaloid. However, some of the above reactions are only empirical and given by other classes of organic compounds such as proteins and glycosides. The most important precipitating reagents are :—Potassium mercuric iodide, phospho-molybdic acid, picric acid, tannic acid, phospho-tungstic acid, silico-tungstic acid, potassium bismuth iodide, chloro-platinic acid, and chloro-auric acid.

GENERAL METHODS OF INVESTIGATION OF THE STRUCTURES OF ALKALOIDS

After the composition and the molar weight are ascertained by the usual methods, the next step is to determine the molecular architecture of the compound *i.e.*, the atomic framework of the molecule. The alkaloids are very complex compounds containing *C*, *H*, *O* and *N* and the determination of their structure involves the elucidation of :—

(*a*) the nature of the carbon framework,

(*b*) the nature of the carbon-nitrogen linkage and the corresponding hetero-system,

(*c*) the nature of the oxygen function grouping.

The general principle employed is to break down the large complex molecules into simple, and readily identifiable molecules. The complete picture of the alkaloidal structure is built up by putting together skilfully the different parts into which the molecule has been thus resolved. For this purpose, the organic chemist employs a number of standard reactions. A few of them will be discussed here.

NATURE OF THE OXYGEN FUNCTION.—Usually the mode of linking of the oxygen atom is established first. When the alkaloid contains oxygen, it is often present as—OCH_3 (methoxy), as free *OH*, and rarely as—*COOR* or —*COOH* group. Dioxymethylene groups also occur frequently. So far, no other alkoxy group has been detected. A ketonic *CO* group is also usually absent. An amide (CONH) linking is also found in a few cases.

THE ESTER GROUPING.—The method employed to detect this group is one of simple hydrolysis ; the alkaloid is heated with water, dilute acid or alkali. This method readily breaks up an ester grouping and converts the alkaloid into its component base and acid parts. It is, however, without action on the rest of the molecule except that in some cases, the basic part may undergo racemisation. Thus, this method leads to the formation of compounds simpler in nature than the original alkaloid molecule. The typical illustrations are :—

ALKALOID	DECOMPOSITION PRODUCTS
piperine	piperidine piperic acid
atropine	tropine tropic acid
cocaine	ecgonine benzoic acid methanol

The hydrolytic processes indicate in many cases the presence of lactone, lactam or betaine, or amide linking.

PHENOLIC HYDROXYL GROUP.—The presence of this group is detected by the solubility of the compound in alkali, its colour reactions with $FeCl_3$ and by the ease of acylation and alkylation. The most commonly used acylating agents are $(CH_3CO)_2O$ in presence of fused *Na*-acetate, or pyridine and benzoyl chloride or its derivative 3,5-dinitro-benzoyl-chloride in pyridine. The alkylation is usually effected by dimethyl-sulphate in alkaline solution or by diazo-methane in ether which is a specific reagent for phenolic groups.

FREE ALCOHOLIC GROUPS :—These are identified by reactions with PCl_5, $SOCl_2$. acetylation or by the action of dehydrating agents like concentrated H_2SO_4, in glacial acetic acid. Dehydration gives rise to an unsaturated compound with the elimination of one molecule of water. Such a conversion has some practical advantages. The unsaturated compound so obtained is naturally more reactive than the original alkaloid and hence, can be submitted to further reactions involving degradations into simpler units. Thus, tropine is dehydrated into tropidine which is further disintegrated into tropinic and tropic acids. Oxidation of the alcoholic group sometimes gives useful results. The quantitative estimation of the free hydroxyl group is carried out by acetylation.

ETHER LINKAGES.—The ether groups most commonly found are : (*a*) methoxy group and (*b*) dioxymethylene or methylene ether group. The detection and quantitative estimation of—OCH_3 groups are accomplished by the methods due to Zeisel. The

alkaloid is heated with the constant boiling mixture of hydriodic acid (b.p. 140°). Methyl iodide is split off and estimated as *AgI*.

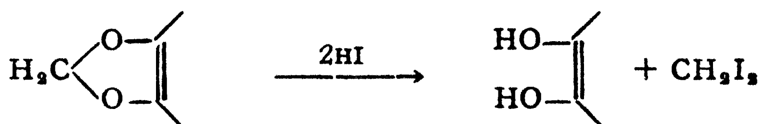




From the amount of *AgI*, the amount and hence, the number of—OCH_3 groups can be easily computed.

The methylene ether grouping : $CH_2\langle^{O-}_{O-}$, is detected

by the gallic acid reagent : a 5% gallic acid solution imparts a green colour to a solution of the compound containing methylene ether group, in H_2SO_4. It is quantitatively estimated by heating with constant boiling HI, when CH_2I_2 is formed.



It can also be quantitatively estimated by heating the ether with sulphuric acid; formaldehyde is formed which is estimated. Use of $NaNH_2$ is suggested for effecting the hydrolysis of methylene ethers. The hydrolysis is carried out in an inert solvent. Recently, constant boiling *HBr* (48%) or anhydrous $AlBr_3$ is employed with some practical advantage by Schopf and Thierfeld and also by Mosetting and Burger.

The results of such demethylation studies have shown that :—

(*i*) papaverine contains four OCH_3 groups,

(*ii*) brucine contains two OCH_3 groups,

(*iii*) quinine contains one OCH_3 group,

(*iv*) piperine contains one methylene ether group.

THE FREE—*COOH* GROUP.—Such a group is readily detected by the solubility of the alkaloid in $NaHCO_3$ solution or in ammonia. Further, the alkaloid can be readily esterified. As a rule the natural product does not carry a free—*COOH* group; it is usually present as a methyl ester as in cocaine. Arecaidine and narceine however. contain free carboxylic groups.

THE-*CO*-GROUP.—Very few alkaloids are ketonic in structure. The detection of the group when present is accomplished by the use of common reagents like semi-carbozide or 2,4 dinitro-phenyl-hydrazine. The alkaloid narceine contains a ketonic group.

NATURE OF NITROGEN FUNCTION.—All alkaloids contain nitrogen. It is usually present as part of a hetero-cyclic system except in the case of phenyl alkylamine types of alkaloids and hence, is only secondary (NH—) or tertiary ($N—CH_3$) or—$N=$. The absence of a free NH_2 group is probably due to methylation by CH_2O present in the plant. Thus, —$N—CH_3$ groups corresponding to $-OCH_3$ are commonly found.

—N-CH_3 GROUPS.—The detection and estimation of methylimino (—NCH_3) group is accomplished by a method due to Herzig and Meyer. The alkaloid is heated with hydriodic acid at 200-300° when CH_3I is split off:—



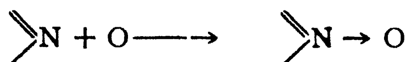
$$>N-CH_3 + HI \longrightarrow >NH + CH_3I$$

The methyl iodide is estimated as AgI and the number of —$N—CH_3$ groups computed as in the case of —OCH_3 group (see above). Distillation of the alkaloid containing —N-CH_3 group with soda-lime, yields methylamine—a reaction often employed for the qualitative detection of —NCH_3 group in an unknown alkaloid. Nicotine, thus, shows the presence of one —NCH_3 group. Sometimes, demethylation at nitrogen (N-$CH_3 \longrightarrow NH$) can be effected with $CNBr$, HNO_2; the compounds thus obtained are called *nor*.

The—OCH_3 group can be detected and estimated in presence of an —NCH_3 group by a combination of Zeisel's method with Herzig and Meyer's method. The methoxyl group is eliminated by hydriodic acid at the latter's boiling-point *i.e.*, at 140°C; at this temperature, the —N-CH_3 group is not attacked at all. Thus, a negative result at the lower temperature may be interpreted to indicate the absence of an —OCH_3 group. However, it must be remembered that no positive conclusion is warranted.

The presence of the tertiary nitrogen atom is also detected by the reaction with methyl iodide. Tertiary bases readily form with

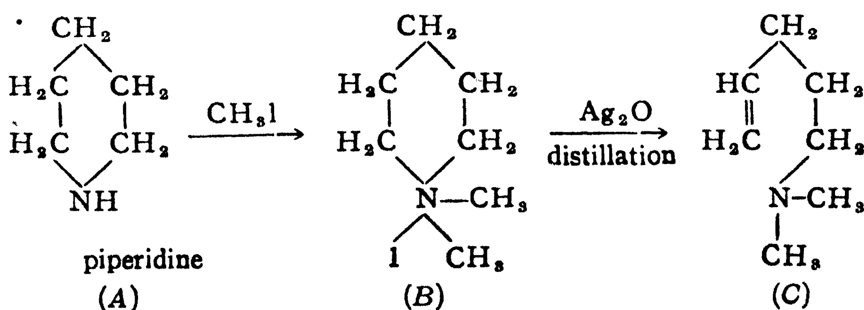
this reagent, crystalline addition compounds: quinine, for example, forms the corresponding crystalline methiodide. Recently, 30 per cent H_2O_2 is sometimes used to detect a tertiary nitrogen atom. The alkaloid under these conditions forms an amine oxide :—



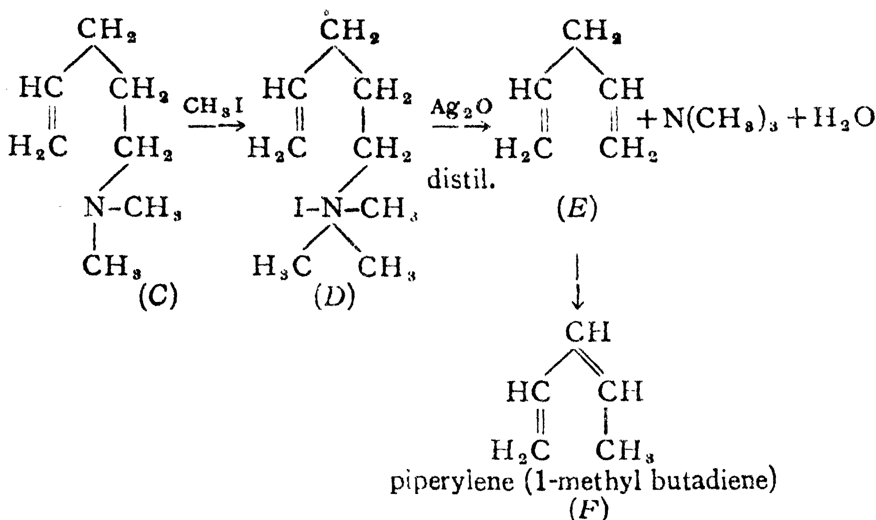
THE HETEROGENEOUS SYSTEMS PRESENT IN THE ALKALOIDS.—As mentioned above, many alkaloids contain their constituent nitrogen as a part of a hetero-cyclic system. A number of methods have been developed for the identification of these hetero-units. The typical and important methods are :—

(*a*) Hofmann's exhaustive methylation.
(*b*) Emde's degradation.
(*c*) Dehydrogenation with zinc or bromine.
(*d*) Reductive degradation.
(*e*) Alkaline fusion.
(*f*) Oxidation.

(*a*) EXHAUSTIVE METHYLATION.—(Hofmann's method). In this method the alkaloid is treated exhaustively with methyl iodide. The quaternary ammonium iodide so formed is heated with silver oxide or dilute alkali to form the corresponding hydroxide. On distillation, the hydroxide decomposes, losing H_2O with the simultaneous fission of the carbon-nitrogen linkage. Piperidine is thus converted into piperylene; the conversion involves several steps :

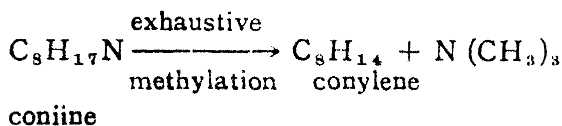


Thus, one of the two C–N linkages is broken. (C) is further treated with CH_3I and subsequently distilled with Ag_2O :—

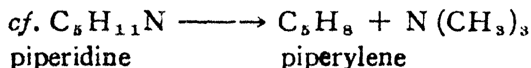


In the above case, where N is linked by two valencies to the ring structure, two methylations and two distillations are essential to eliminate the nitrogen atom. The latter is removed as $N\ (CH_3)_3$ and the carbon framework is revealed as an unsaturated, diolefinic system : (E) and (F); at the same time, there occurs no structural alteration in the remaining part of the molecule. The unsaturated system is then reduced and converted into a saturated compound of known structure; the mode of linking of the carbon atoms is thus indicated. Similarly, the mode of linking of the nitrogen atom with the rest of the molecule is thus clearly exposed and the nature of the hetero-system established.

The alkaloid coniine, on exhaustive methylation, gives conylene :—



$$\underset{\text{coniine}}{C_8H_{17}N} \xrightarrow[\text{methylation}]{\text{exhaustive}} \underset{\text{conylene}}{C_8H_{14}} + N\,(CH_3)_3$$



$$cf.\ \underset{\text{piperidine}}{C_5H_{11}N} \longrightarrow \underset{\text{piperylene}}{C_5H_8} + N\,(CH_3)_3$$

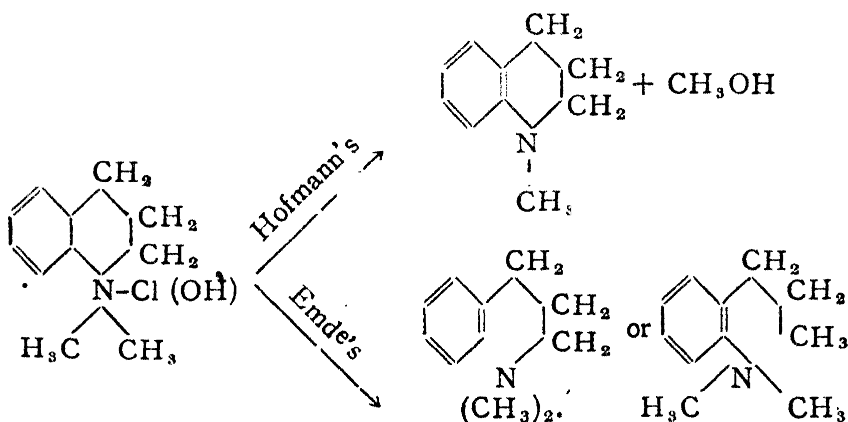
These results indicate that coniine, like piperidine contains a reduced pyridine system.

This method can be extended to the investigation of the acids, obtained as products of oxidation of some alkaloids

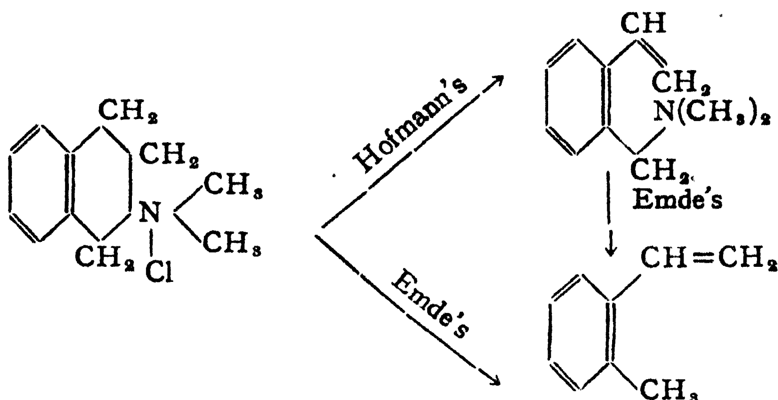
Tropinic acid, for example, on exhaustive methylation, gives a di-olefinic dibasic acid, which, on reduction with sodium and alcohol gives pimelic acid $(CH_2)_5\ (COOH)_2$. These results indicate that the seven carbon atoms in tropinic acid form a single straight-chain system.

The above degradation results of exhaustive methylation followed by reduction, have also additional practical importance. They give successfully a clue to a possible synthesis of the alkaloid by going up in the reverse direction.

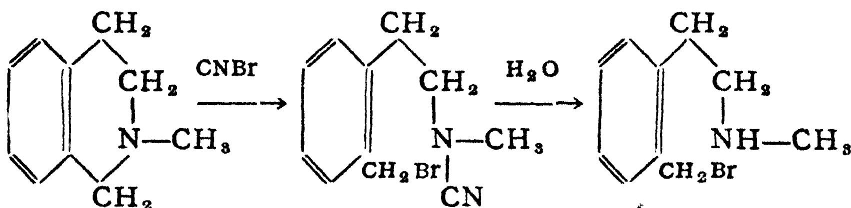
(*b*) EMDE'S METHOD.—Hofmann's degradation, however, has some important practical limitations. It is applicable only to hydrogenated nitrogenous nuclei, but fails with hydrogenated quinoline derivatives. This method has been fruitfully replaced by Emde's degradation method. This consists in the treatment of the quaternary halide in alcoholic or aqueous solution with sodium amalgam. This degradation may yield the same products as Hofmann's but it succeeds with ring systems that cannot be opened up by Hofmann's method. Thus, we have :—



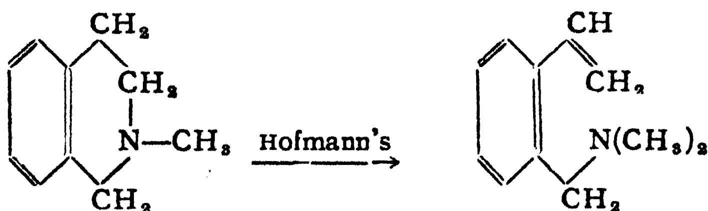
(2) With tetra-hydro-dimethyl iso-quinoline halide, the disintegration goes further with Emde's method than with that of Hofmann. Emde's process involves (*i*) *degradation* and (*ii*) ***reduction*** of the molecule. The reducing agent is the sodium amalgam.



There are other methods devised for the opening up of heterocyclic ring systems. The most useful are those due to Von Braun. In one method, he uses cyanogen bromide (*CNBr*). The latter readily reacts with the tertiary nitrogen atom with the fission of one of the *C-N* linkages: the mode of addition is that the *CN* group becomes attached to the nitrogen atom while *Br* attaches itself to the carbon atom: this is the method used in the case of tertiary amines.

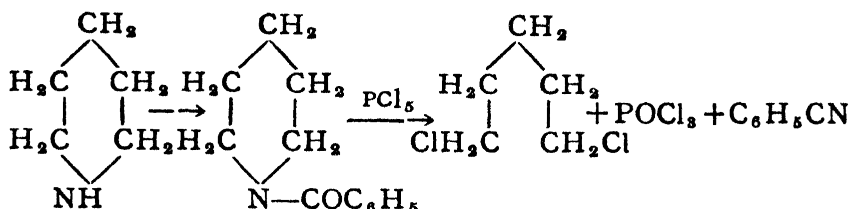


The secondary amine thus formed can be degraded further, it opens up the ring at a different point, for the iso-quinoline system is degraded by Hofmann's method as follows:



Another advantage of Von Braun's method is that it succeeds with compounds where Hofmann's fails.

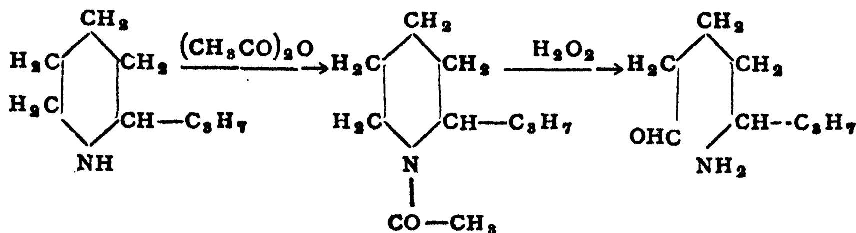
The other method of Von Braun which is applicable to secondary amines consists in the action of phosphorus pentachloride (PCl_5) or pentabromide (PBr_5) on the *N*-benzoyl derivative of the alkaloid. A high temperature is used and the reaction proceeds in two steps: A dichloroderivative ($CO \rightarrow CCl_2$) is first formed which is then decomposed to give α-ω dihalogen derivative; with piperidine we have:



Coniine, thus on distilation with PCl_5, gives 1.5 dichloro-octane.

When PBr_5 is employed, the corresponding dibromo derivative is obtained. This is one of the practical methods of preparing a 1.5 (α-ω) dihalogen paraffin derivative.

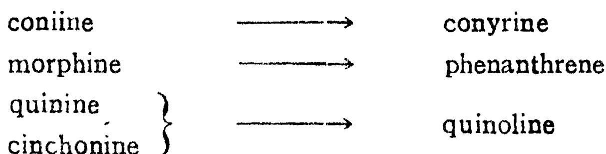
There is still another method of opening up the nitrogenous ring system. It is one of controlled oxidation. The usual oxidising agents used for this purpose are hydrogen peroxide and potassium permanganate. The secondary base (*NH*-grouping) is first acetylated and then subjected to oxidation. The *C*·*N* linkage is broken up with the formation of an aliphatic aminoaldehyde. Coniine, thus, on oxidation with H_2O_2, gives the 5-amino-*n*-octoic-aldehyde:—



Lastly, the nitrogenous rings, even unhydrogenated can be opened by heating them with con. HI at 300°; coniine thus is converted into *n*-octane and ammonia.

(*c*) DEHYDROGENATION.—The alkaloid is heated with bromine, sulphur or selenium; phosphoric acid (meta) is often employed; dehydrogenation is effected with the elimination of the excess of hydrogen in the molecule. At the same time, the less enduring part of the complex alkaloidal molecule is completely disintegrated and the reaction product contains some stable nucleus such as pyridine, quinoline, iso-quinoline etc. These degradations can, therefore, be employed to determine the nature of the heterocyclic system present in the alkaloid.

(*d*) REDUCTIVE DEGRADATION.—In this method the alkaloid is both reduced and degraded simultaneously. The most common process is to distill the alkaloid over hot zinc dust. The phenolic hydroxyl groups are replaced by H and if the compound is very rich in hydrogen, dehydrogenation is also effected. Finally, the molecule suffers disintegration to form stable ring systems. Thus we have:



Other reductive methods employed are: (*a*) sodium and alcohol and (*b*) catalytic hydrogenation. Such methods as these, have helped to establish the relationships between alkaloids that are isomers owing to a difference in the location of unsaturation in the molecule or those that differ in degrees of oxidation.

(*e*) ALKALINE FUSION.—This is a very drastic method often used to break down the complex alkaloid molecule into simpler compounds. The alkaloid is fused with potassium hydroxide, leading to the isolation of stable units which survive such a drastic treatment. Usually, the nitrogenous hereto-systems are isolated at the end of the degradation. Papaverine thus, on fusion with alkali, gives dimethoxy-isoquinoline and homo-veratrole. However, such a drastic treatment is likely to be accompanied by intramolecular rearrangement reactions. This would vitiate our conclusions as

regards the structure of the molecule involved (*cf.* the preparation of resorcinol from 1–4 disulphonic acid of benzene).

The foregoing methods have been applied to the investigation of many of the natural alkaloids and the hetero-cyclic units present in them have been identified.

ALKALOID		HETERO-UNIT
coniine, nicotine, piperine	⟶	pyridine
quinine, chinchonine	⟶	quinoline
papaverine	⟶	iso-quinoline
atropine, cocaine	⟶	tropine

(Morphine on distillation with zinc dust gives phenanthrene a condensed nuclear system not containing nitrogen).

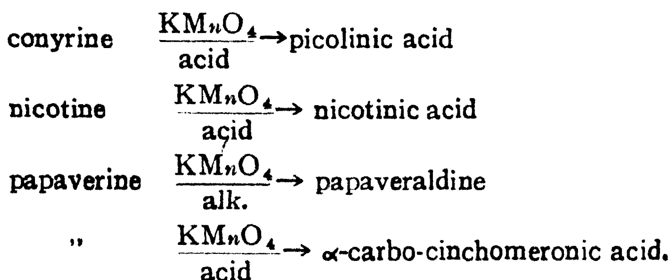
(*f*) OXIDATIVE DEGRADATION.—The final stages in the determination of the constitution of an alkaloid are those which involve oxidation methods. They include studies of the products of controlled and regulated oxidation of the complex molecules. The alkaloids or their transformation products very en contain such groups as $C=C$, $CHOH$, and $-NCH_3$. These offer very vulnerable points of attack by oxidants. Several oxidising agents have been employed. The choice of a particular oxidant is guided by the degree of degradation desired and the stability of the structure of the molecule involved, With chromic acid and potassium permanganate, it is possible to oxidise the molecuie in stages, until the most resistant parts remain unattacked. Mild oxidising agents, for example, silver acetate, mercuric acetate and alkaline potassium ferricyanide, may bring about partial oxidation. The use of pottassium permanganate has special practical advantages. It can be employed under alkaline and acid conditions. In the former case, a double bond present is attacked with the formation of a glycol. The glycol is further oxidised by acid potassium permanganate or acid chromic, which leads to the cleavage of the molecule at the point of the double bond. Such results furnish very important clues regarding the structural pattern of the complex molecule. Also, potassium permanganate shows the

peculiar property of oxidising a methyl group away from a nitrogen atom. Hydrogen peroxide, alkaline hypobromites, lead peroxide, nitric acid etc., have also found fruitful applications in some typical cases.

The oxidation may involve the following different types of changes:

(*i*) oxidation of a double bond (O_3, $KMnO_4$)
(*ii*) oxidation of $CH_2 \longrightarrow CO$ (alk. $KMnO_4$)
(*iii*) oxidation of $CHOH \longrightarrow CO$ (CrO_3)
(*iv*) oxidation of $CH_3 \longrightarrow COOH$ ($KMnO_4$)
(*v*) opening up of the hetero ring (H_2O_2)

The following are a few important illustrations of the use of the above oxidation methods:



conyrine $\xrightarrow[\text{acid}]{KMnO_4}$ picolinic acid

nicotine $\xrightarrow[\text{acid}]{KMnO_4}$ nicotinic acid

papaverine $\xrightarrow[\text{alk.}]{KMnO_4}$ papaveraldine

" $\xrightarrow[\text{acid}]{KMnO_4}$ α-carbo-cinchomeronic acid.

The results in each case, reveal the fundamental structural system present in the individual alkaloid. Thus in these reactions we have an excellent method of following the successive and step-wise degradation of the highly complex alkaloid into relatively simpler molecules, through difinite intermediate stages. Such information is at once helfpul to build up a picture of the structural pattern of the alkaloid. The structure of an alkaloid arrived at by the exhaustive analytical evidence based on the foregoing methods, is only tentative. The final confirmation of the structure must come by a complete or total synthesis of the alkaloid.

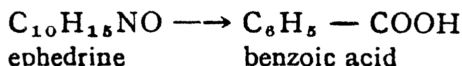
In the following pages, a few of the more important and common alkaloids will be discussed. The choice will be limited to the representative of the different hetero-cyclic systems. The phenyl-alkyl-amine group of alkaloids, ephedrine and hordenine will also be treated here.

ALKALOIDS WITH OPEN CHAIN AMINE STRUCTURE

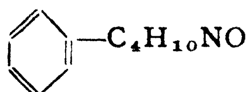
The most common alkaloids belonging to the phenyl-alkyl-amine group are ephedrine and hordenine. Both possess typical alkaloidal properties.

EPHEDRINE.—Ephedrine is present in the Chinese herb Ma. Huang-Ephedra vulgaris. It is usually accompanied by other alkaloids structurally related to it; some of them are *d*-pseudo-ephedrine, *l*-methyl-ephedrine, *d*-methyl ephedrine etc. They are collectively referred to as Ephedra bases. It was first isolated from the herb by Nagai. Ladenburg succeeded in elucidating the structure of the *d*-isomer. It is based on the following analytical reactions. Ephedrine has the molecular formula $C_{10}H_{15}NO$.

Nature of the carbon-skeleton.—On oxidation, ephedrine gives benzoic acid or benzaldehyde.

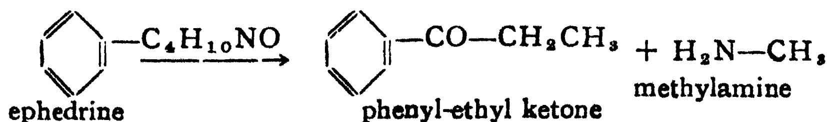


This points to the presence of an aromatic nucleus with one side-chain in the molecule. Ephedrine may, therefore, be represented as :—

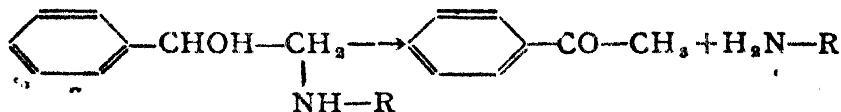


Nature of the side-chain.—(i) Nature of the nitrogen atom: Ladenburg has shown that ephedrine is a secondary base, as it readily gives a nitroso derivative and that on boiling with concentrated hydrochloric acid, the nitrogen atom is eliminated as methylamine. These results, thus, indicate the presence of $NH—CH_3$ group in the molecule. This indicates the presence of an alcoholic hydroxyl group in addition to the NH-group which would form a benzoyl derivative.

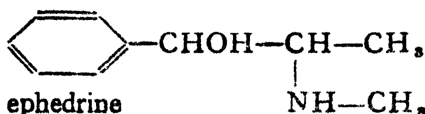
(ii) The location of the hydroxyl group—The hydrochloride of ephedrine, on heating with hydrochloric acid suffers the "*hydramine cleavage.*" Thus, Schmidt found that ephedrine gives phenylethyl-ketone and methylamine :—



The above fisson is characteristic of compounds with a hydroxyl group in α-position to a benzene nucleus and an amino or substituted amino group in the β-position.

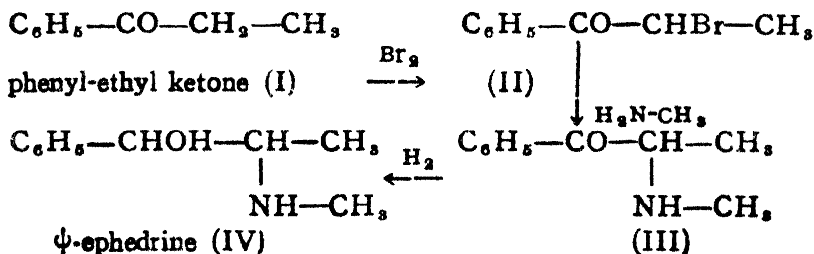


All these facts lead to the formulation of ephedrine :—



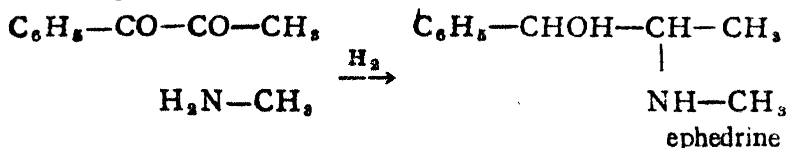
The above structure has been confirmed by several independent syntheses :—

1. *Eberhard and Fourneau synthesis.*—The starting-point is phenyl-ethyl ketone (I). On bromination, the bromo-derivative (II) is obtained which, on treatment with methylamine, gives the ketonic derivative (III). The latter, on reduction, gives the φ ephedrine (IV). Schematically, we have :—



On prolonged boiling with *HCl*, the pseudo compound is changed into ephedrine.

2. *Manske and Johnsen's synthesis.*—This is the most simple and elegant synthesis. Phenyl-methyl diketone is catalytically reduced in the presence of methylamine and methanol when ephedrine is formed in good yield :—

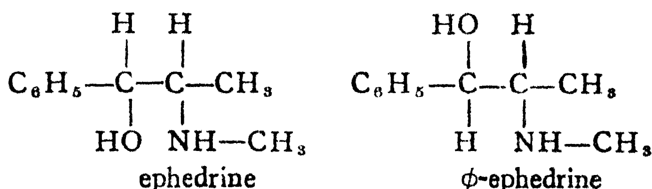


A recent synthesis more economical has been reported. Sugar is fermented in presence of C_6H_5CHO, when $C_6H_5CHOH—COCH_3$

is formed through an enzymatic condensation of C_6H_5CHO and CH_3CHO. The ketone thus obtained is then treated with CH_3NH_2 in presence of H_2 to give *l*-ephedrine directly. Thus the wasteful method of converting the *dl* compound into the *l* isomer is avoided.

Ephedrine is a compound with a melting-point of 40°. It is *l*-rotatory in alcoholic solution but *d*-rotatory in water. It finds use in medicine as a mydriatic. It is also used in the treatment of asthma and can be administered orally. It causes rise in blood-pressure like adrenaline.

Relation between ephedrine and pseudo-ephedrine :—Ephedrine and pseudo-ephedrine are stereo-isomers. They differ in the configurations of *H* and *OH* on the α-carbon atom :—

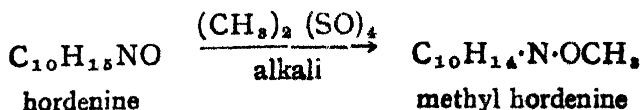


l-Ephedrine is converted into pseudo-ephedrine by acids, but on prolonged heating with hydrochloric acid, the change is reversed.

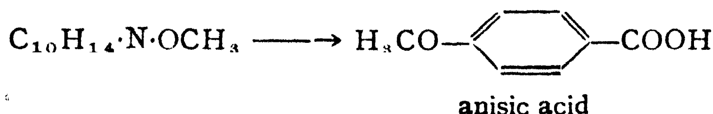
Recently synthetic ephedrine called ***ephetonine*** is obtained in large quantities and used extensively in the treatment of asthma and hay fever. It is racemic.

HORDENINE.—Leger discovered that the embryo of barley contains a nitrogenous '*active principle*' and isolated from it a crystalline compound melting at 118°. He called it ***hordenine.*** It is also present in the several varieties of the Anhalonium plant. Hence, it is also named ***anhaline.*** The natives of Mexico and the South West of United States of America use the dried slices of the plant as intoxicants.

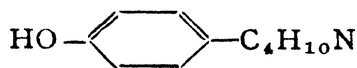
STRUCTURE :—The molecular composition is $C_{10}H_{15}NO$. On methylation with dimethyl sulphate and alkali, a monomethyl derivative is obtained :—



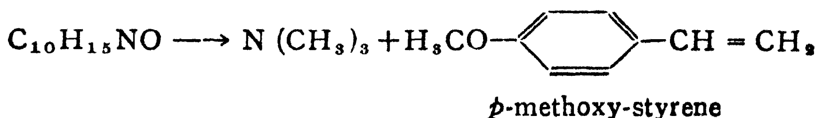
This indicates the presence of one *OH* or *NH* group. The methyl derivative, on oxidation with potassium permanganate in alkaline solution, yields anisic acid :—



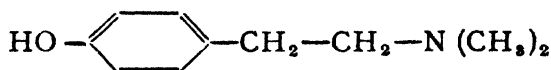
Hordenine, therefore, would be represented by :—



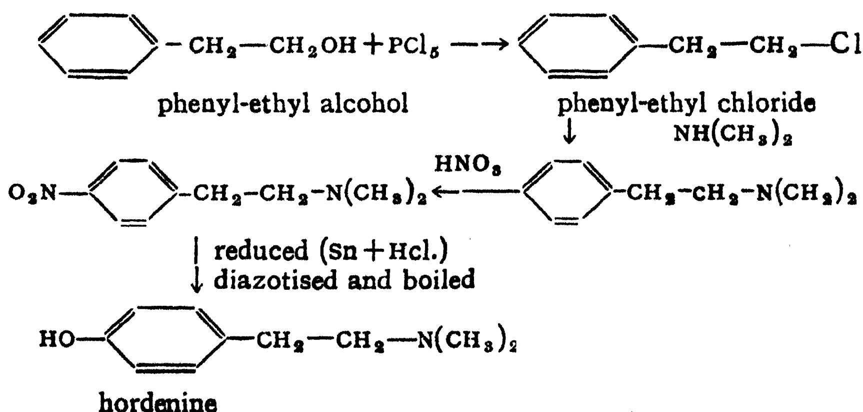
The nature of the side-chain, $C_4H_{10}N$:—On exhaustive methylation, hordenine gives tri-methylamine, and *para*-methoxy-styrene :



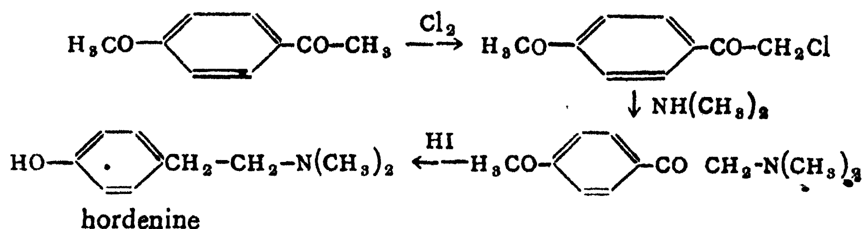
These results, thus, confirm the nature of the carbon framework including the side-chain and also reveal the position of nitrogen atom. Hence, hordenine would be represented by :—



It has been confirmed by numerous syntheses. Barger starts from phenyl-ethyl alcohol. The different steps involved can be formulated as follows :—



Another synthesis employs *p*-methoxy-aceto-phenone as the starting-point. The various steps are :—



hordenine

In the last step, hydriodic acid effects both demethylation and reduction of the molecule.

Recently, Von Braun and collaborators have obtained analogous compounds in which the $N(CH_3)_2$ group is further removed from the benzene nucleus. Another modification introduced by them is the changing of the *OH* group from the *para* to the *ortho* position. The effects of such variations on the physiological properties have been investigated.

ANHALINE.—As mentioned earlier, it is one of the basic substances isolated from the cactus of anhalonium family. The other related bases are mezcaline, anhalonine and anhalamine. Spath has shown that anhaline obtained from this source is identical with hordenine from the germinating barley. The structural formulas of many of the other closely associated bases from this cactus, have been established by syntheses by Spath and his collaborators.

ALKALOIDS WITH PYRIDINE RING

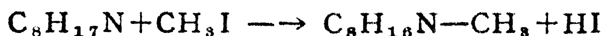
Many alkaloids are known which contain the pyridine ring. The most important are Hemlock, Pomegranate, Pepper, Castor-bean and Areca nut alkaloids.

HEMLOCK ALKALOIDS.—Coniine is the chief alkaloid of the hemlock or spotted cowbane. It occurs associated with four other closely related alkaloids in combination with malic and caffeic acids. The other related alkaloids are: γ-coniceine, conhydrine, pseudo-conhydrine, and *N*-methyl-coniine. Coniine is obtained as follows: the seeds are extracted with dilute acetic acid and the solution of the acetate is decomposed with magnesia, and the alkaloids extracted with ether. In another method, the raw material (fruit and seed) finely powdered, is distilled with KOH' It is *d*-rotatory and is a strongly alkaline liquid b.p. 167° and possesses a burning taste. It gives no colour reaction with H_2SO_4 nor with HNO_3. With Na-nitroprusside, a deep red colour is formed, which disappears on warming and reappears on cooling.

Structure :—It was first isolated in 1831. Its composition and structure have been determined by Hofmann and Ladenburg; it was the first alkaloid to be synthesised. The constitution is based on the following analytical and synthetic evidence :

(*a*) Nature of the N atom and the hetero-cyclic system :

Coniine reacts with methyl iodide to form an *N*-methyl derivative :—



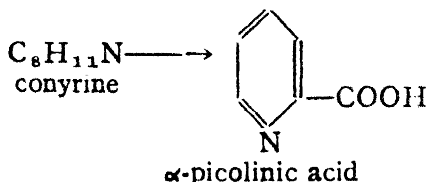
$$C_8H_{17}N + CH_3I \longrightarrow C_8H_{16}N{-}CH_3 + HI$$

i.e. coniine is a *secondary* base. It also reacts with nitrous acid and also gives a benzoyl derivative. The nature of the heterosystem is revealed by results of the dehydrogenation and oxidation reactions. The hydrochloride of coniine, on distillation with zinc dust, gives a new basic compound *conyrine* : (dehydrogenation takes place).

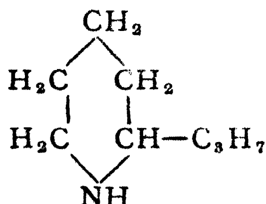


$$\underset{\text{coniine hydrochloride}}{C_8H_{17}N{-}HCl} \longrightarrow \underset{\text{conyrine}}{C_8H_{11}N} + 6H$$

Conyrine is also formed from coniine, on dehydrogenation with silver acetate. Conyrine can be readily reduced back to coniine (racemic form.) (cf. piperidine ⇄ pyridine). Conyrine is a *tertiary* base forming a crystalline additive compound with methyl iodide. On oxidation with potassium permanganate, conyrine gives, α-picolinic acid :—



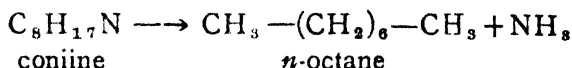
Now conyrine is obtained from coniine by dehydrogenation, hence, coniine may be represented by :—



i.e. an α-propyl-piperidine. The hetero-system present is that of *pyridine*.

(*b*) *Nature of the side-chain* $-C_3H_7$:—Theoretically, there are two possibilities : (*a*)—C—C—C the normal propyl, and (*b*)—C$<^{C}_{C}$ the iso-propyl. The exact nature of the side-chain in the coniine molecule was elucidated by one of the following degradation methods.

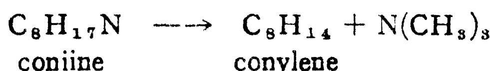
(*i*) Reduction with concentrated *HI* : coniine, when heated with hydriodic acid at 300° gives ammonia and *n*-octane :—



$$\underset{\text{coniine}}{C_8H_{17}N} \longrightarrow \underset{n\text{-octane}}{CH_3-(CH_2)_6-CH_3} + NH_3$$

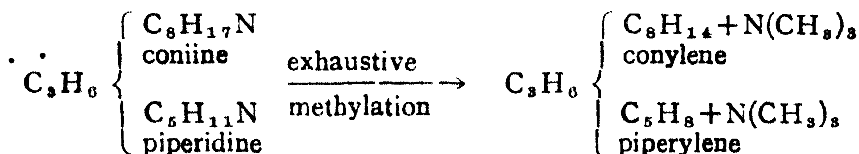
i.e., the eight carbon atoms, five from the pyridine nucleus and three from the side-chain form a straight-chain system. The side-chain must, therefore, be —C—C—C *i.e.* the normal propyl group.

(*ii*) Exhaustive methylation :—results of exhaustive methylation also point to the same conclusion. Coniine, when thus degraded yields conylene and $N(CH_3)_3$:—



$$\underset{\text{coniine}}{C_8H_{17}N} \longrightarrow \underset{\text{conylene}}{C_8H_{14}} + N(CH_3)_3$$

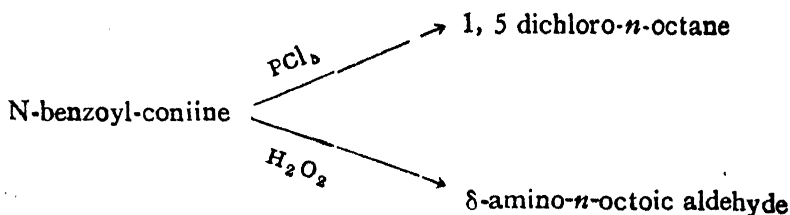
Conylene, on reduction, gives *n*-octane. An inspection of the composition of the products of exhaustive methylation of piperidine and coniine, reveals the simple relationship between the two :—



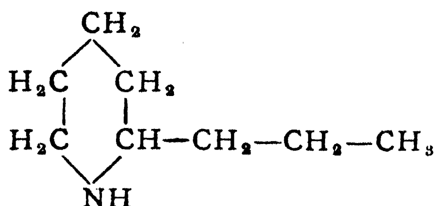
$$C_3H_6 \left\{ \begin{array}{l} \underset{\text{coniine}}{C_8H_{17}N} \\ \\ \underset{\text{piperidine}}{C_5H_{11}N} \end{array} \right. \xrightarrow[\text{methylation}]{\text{exhaustive}} C_3H_6 \left\{ \begin{array}{l} \underset{\text{conylene}}{C_8H_{14}} + N(CH_3)_3 \\ \\ \underset{\text{piperylene}}{C_5H_8} + N(CH_3)_3 \end{array} \right.$$

i.e. the difference between the composition of conylene and piperylene (which is C_3H_6) is the same as exists between coniine and piperidine. Hofmann, therefore, inferred that coniine must be a simple propyl derivative of piperidine; Konig concluded that it was *n*-propyl-piperidine.

Results of von Braun's method using PCl_5 and those of oxidation with hydrogen peroxide, confirm the above structure :



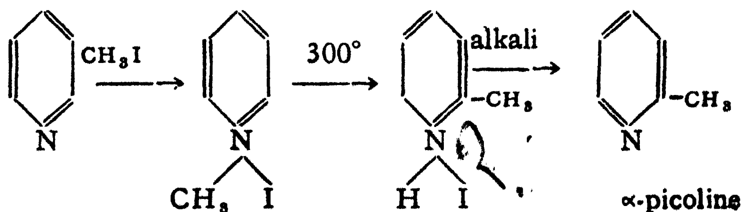
All this analytical evidence clearly leads to the formulation of coniine as *n*-propyl piperidine :—



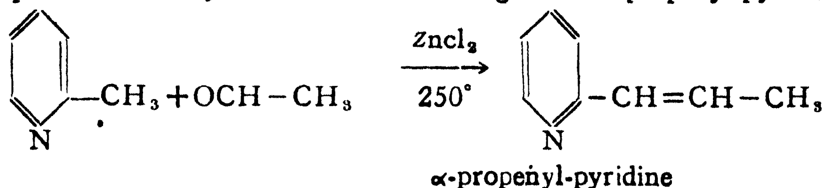
Confirmation by synthesis.—Ladenburg achieved a complete synthesis of coniine. Starting from CS_2, he obtained acetone which was converted into glycerol; the latter was changed into $CN{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$; on reduction, penta-methylene-diamine was obtained, di-hydrochloride of which on distillation gave piperidine. The latter on oxidation gave pyridine. (Pyridine can be synthesised by passing a mixture of acetylene and hydrocyanic acid, through a red hot tube : $2C_2H_2 + HCN \rightarrow C_5H_5N$.)

Pyridine was then converted into coniine by a series of reactions :

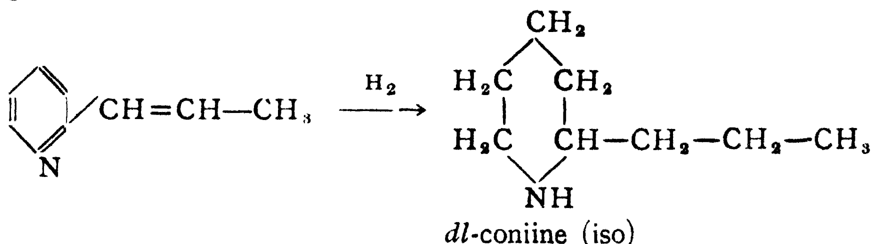
(*a*) α-picoline was synthesised from pyridine.



(*b*) α-picoline was condensed with acetaldehyde (paraldehyde) in presence of anhydrous zinc chloride to give the α-propenyl-pyridine.

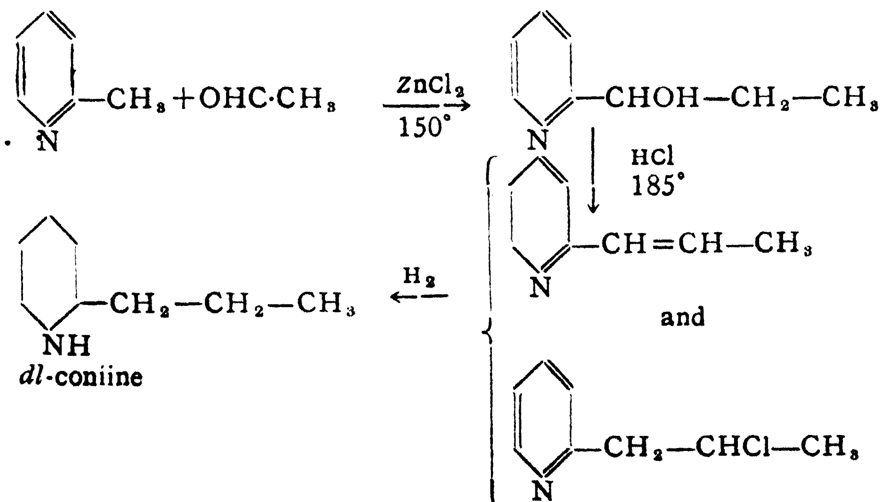


(*c*) reduction of the propenyl-pyridine in alcohol with sodium, gave *dl*-coniine.



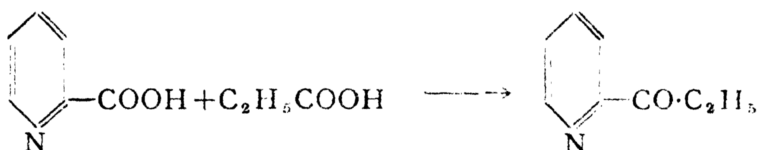
dl-Coniine was obtained by Ladenburg by heating the above product to 300°.

The yields, however, were poor. In a recent modification, the condensation is effected in two steps. α-Picoline is condensed with paraldehyde and zinc chloride at 150° to give the hydroxy derivative, which is then dehydrated with con. HCl at 185°; α-propenyl-pyridine and some 2-chloro-propyl-pyridine are formed which are both reduced to *dl*-coniine, with Na-amalgam and alcohol.



The yield of *dl*-coniine is further improved by reducing the hydroxy compound with HI and P and subsequent treatment with Zn dust and water; the racemic was resolved by means of *d*-tartaric acid. *d*-Coniine thus obtained was identical with the natural product.

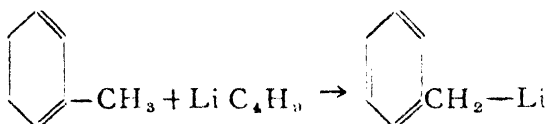
Another synthesis is due to Engler and Bauer. An equimolar mixture of calcium salts of α-picolinic and propionic acids is distilled when *α-ethylpyridyl* ketone is formed :—



Cf -the formation of acetophenone from ca-benzoate and ca-acetate.

The ketone on reduction with Na-amalgam gives hydroxy propyl pyridine, which on further reduction with Na and alcohol gives *n*-propyl-piperidine *i.e.* *dl*-coniine (very small yield).

In a recent synthesis, α-picoline is treated with LiC_4H_9 in benzene to give the Li-derivative.

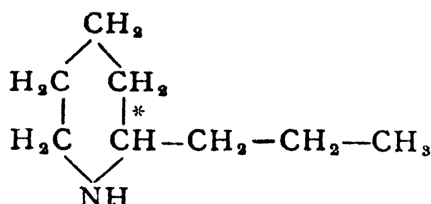


The latter on treatment with C_2H_5Br and subsequent reduction with Na and alcohol yields *dl* coniine.

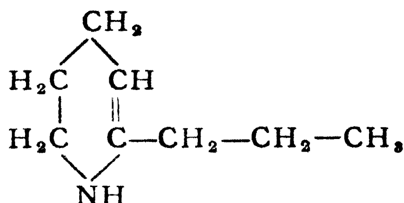
γ-CONICEINE.—It is an alkaloid closely associated with, and structurally related to coniine. Its composition is $C_8H_{15}N$ and hence, contains two hydrogen atoms less than coniine. On reduction, it is changed into *dl*-coniine. It can be readily obtained from chloro-or-bromo-coniine by the action of alcoholic alkalies. Distillation of the base with zinc dust gives conyrine.

The position of the double bond.—The above relationships definitely indicate that the structural formula of γ-coniceine is the same as that of coniine with a double bond in the molecule. The exact position of the double bond is based on the following facts :— (*a*) γ-Coniceine is optically inactive and hence, the asymmetric carbon atom of coniine must be involved in the unsaturation. (*b*) It is also a secondary base: part of the pyridine system is thus hydrogenated.

Now, coniine is :—

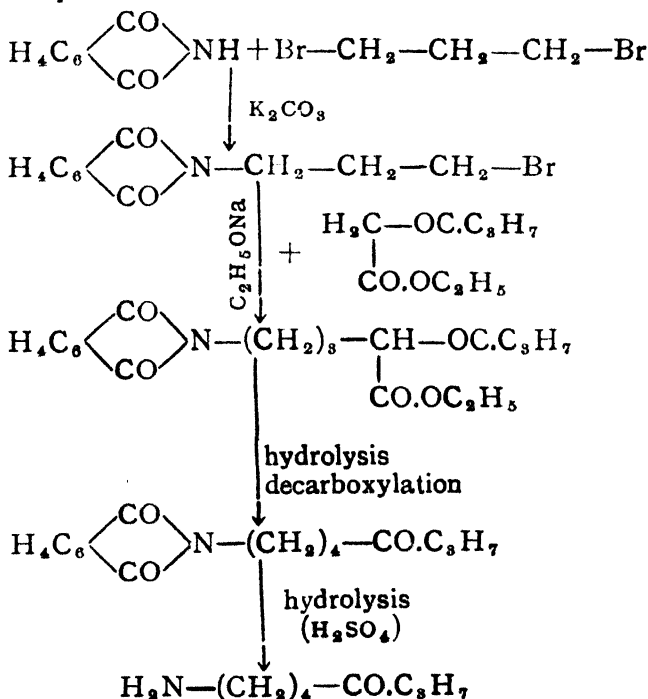


The carbon atom marked with asterisk is asymmetric. Hence, γ-coniceine will have to be represented by :—

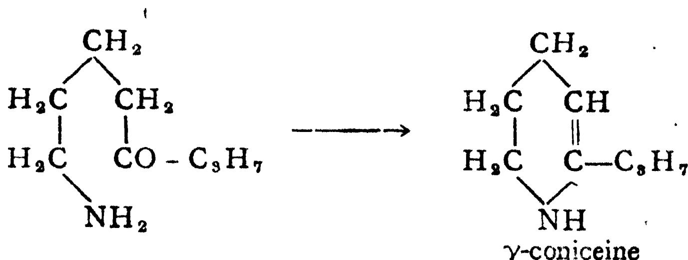


This structure is confirmed by Gabriel's synthesis :—

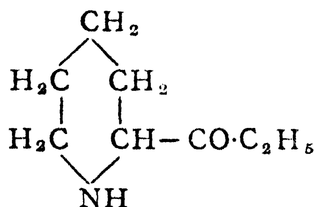
(*a*) Preparation of a ketone-amine :—



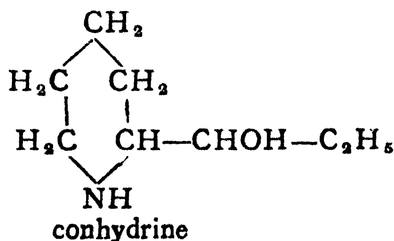
(*b*) Cyclisation of the ketone-amine : The ketone-amine, sc obtained readily suffers ring-closure to give γ-coniceine :—



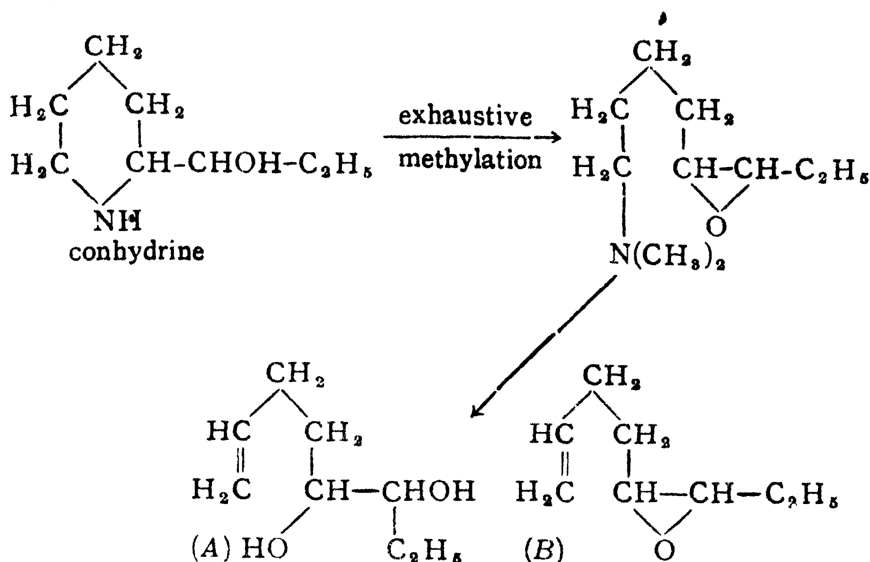
CONHYDRINE.—It possesses the molecular composition $C_8H_{17}NO$. It is the oxygen containing alkaloid of the Hemlock. It is a secondary base and carries an alcoholic hydroxyl group. It thus appears to be hydroxy-coniine. That the hydroxy group is present in the side-chain is indicated by the formation of a ketonic derivative, conhydrinone, on mild oxidation. The exact position of the hydroxyl group has been established by the identity of the ketone with synthetical α-piperidyl propanone. The latter has the structure :—



Also *N*-methyl conhydrinone has been obtained as a product of methylation and subsequent oxidation of conhydrine. Hess and Gram, and later on Spath and Adler have proved the identity of the compound with the synthetic α-*N*-methyl-piperidyl-propanone. Therefore, conhydrine can be best represented by :—

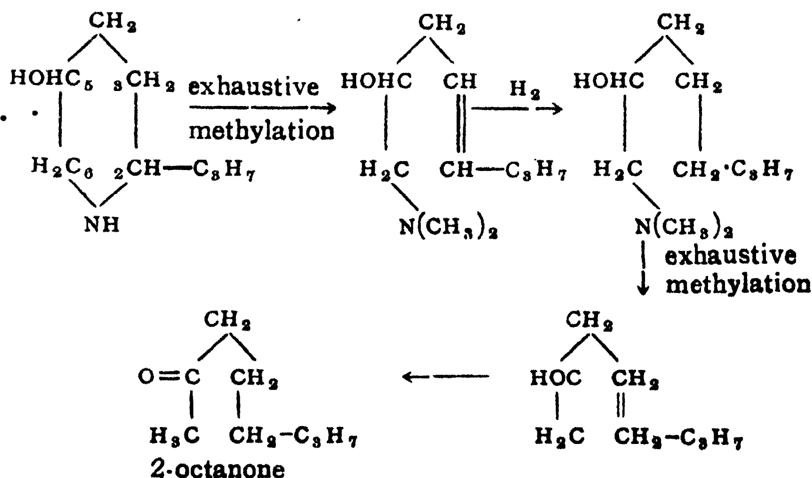


The above structure is also in agreement with the degradation results of Hofmann's exhaustive methylation method :—



The compound A, on catalytic hydrogenation (Pd+C) gives a dihydro derivative which on oxidation gives *n*-valeric acid; on the other hand, the compound A on oxidation with $KMnO_4$ and H_2SO_4, gives succinic acid and propionaldehyde. These results thus conclusively establish the structure assigned to conhydrine.

PSEUDO-CONHYDRINE.—It is a structural isomer of conhydrine. The difference is due to the position of the hydroxyl group. Spath has formulated a structure for pseudo-conhydrine. It is based on the results of Hofmann's degradation method. It is revealed that the hydroxyl group, present in the piperidine system, is in position 5. The course of the degradation of the molecule is :—



The formation of 2-octanone decisively proves the location of the hydroxyl group on carbon atom 5, of the piperidine system.

N—methyl coniine is the *N*-methyl derivative of coniine from which it can be readily obtained by direct methylation. It occurs in nature, in both the optical active forms.

POMEGRANATE ALKALOIDS :—Tanret (1877) has reported the existence of four alkaloids in the bark of the pomegranate tree. They are pelletierine, pseudo-pelletierine, iso-pelletierine and methyl pelletierine. They are so named in honour of the French alkaloid chemist Pelletier.

PSEUDO-PELLETIERINE.—The chief alkaloid is pseudo-pelletierine. Pseudo-pelletierine possesses the molecular composition $C_9H_{15}NO$. Its structure has been elucidated by the researches of Cimiacian and Silber, Piciinini and Willstatter. It is based on the results of degradation and synthetic methods.

(a) *Nature of nitrogen atom* :—Pseudo-pelletierine forms a crystalline methiodide, with methyl iodide. Hence, the nitrogen atom is tertiary.



$$C_9H_{15}NO + CH_3I \longrightarrow C_9H_{15}NO.CH_3I$$

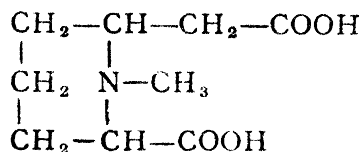
(b) *Nature of oxygen atom* :—With hydroxylamine, pseudo-pelletierine gives an oxime, and on reduction, forms a secondary alcohol. Hence it contains a ketonic group. Further, the formation of dibenzylidene or di-iso nitroso derivatives with benzaldehyde and nitrous acid respectively, indicates that the *CO* group is between two methylene groups ($CH_2—CO—CH_2$).

(c) *Nature of the hetero system* :—On oxidation, pseudo-pelletierine is converted into a dibasic acid, methyl-granatic acid—



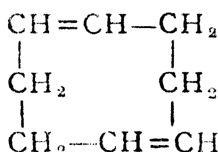
$$C_9H_{15}NO \xrightarrow{O_2} C_7H_{14}N{\cdot}(COOH)_2$$

The latter contains the same number of carbon atoms as pseudo-pelletierine. Hence it must be a cyclic ketone. On exhaustive methylation, the methylgranatic acid gives an unsaturated dibasic acid which on reduction, forms suberic acid : $HOOC{\cdot}(CH_2)_6{\cdot}COOH$. Further, methyl-granatic acid can be shown to carry the piperidine system. It thus, possesses the constitutional formula :—

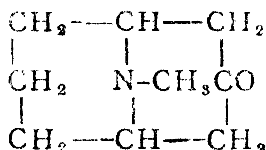


The above formula explains satisfactorily, the formulation of an eight carbon atom system, from methyl-granatic acid by exhaustive methylation.

Pseudo-pelletierine must, therefore, contain the same carbon-nitrogen skeleton. But it represents a closed ring system, as Willstatter has been able to degrade pseudo-pelletierine to cyclo-octadiene :—

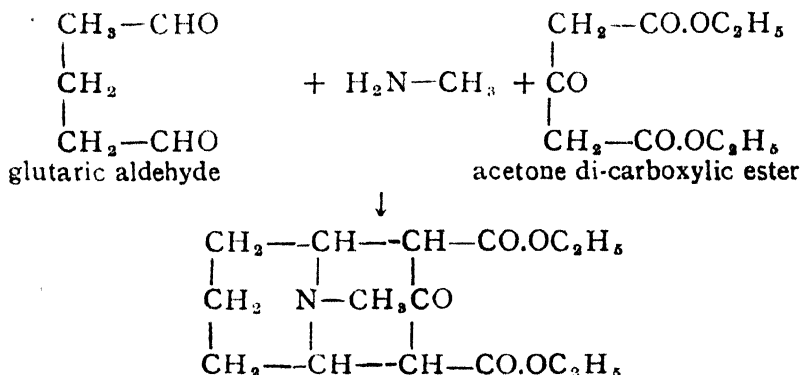


Pseudo-pelletierine can, hence, be formulated as :—



The above formula is in agreement with the conclusions drawn under (*b*) regarding the existence of—$H_2C—CO—CH_2$—grouping. Further it indicates a close relationship to tropinone (*q.v.*) whose higher homologue it is.

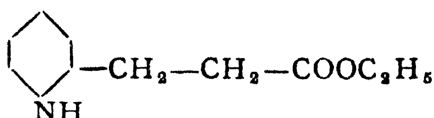
Synthesis :— An elegant synthesis based on speculation regading the mode of formation of the alkaloid in the plant has been achieved by Menzies and Robinson. It consists in the condensation of glutaric aldehyde, acetone di-carboxylic ester and methylamine (*Cf.* the synthesis of tropinone).



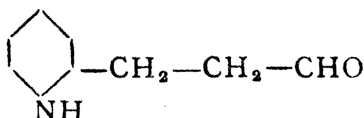
On acidification and subsequent distillation in high vacuum, pseudo-pelletierine is formed; the ester groups are hydrolysed and at the same time decarboxylation takes place.

Pelletierine.—It has the molecular composition, $C_8H_{15}NO$. Its constitution is based on the following evidence.

(*a*) It forms an oxime, which on dehydration with PCl_5 gives the nitrile hydrolysable to an acid, the ethyl ester of which is identical with the synthetic ethyl ester :

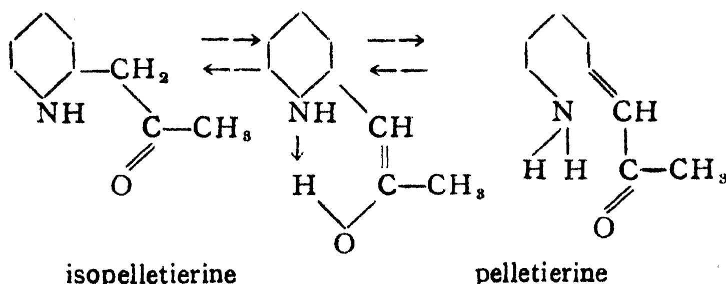


Hence the oxygen atom in pelletierine is present as an aldehyde, and pelletierine must be



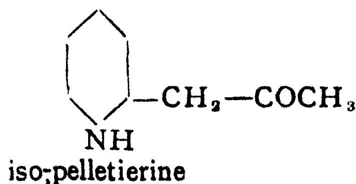
(*b*) the above structure is confirmed by the reduction of pelletierine hydrazone to *dl*-coniine, with Na-ethoxide.

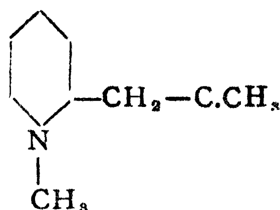
The above structure has now been questioned by Galinovsky. He has proposed that pelletierine is related to isopelletierine in the following way :—



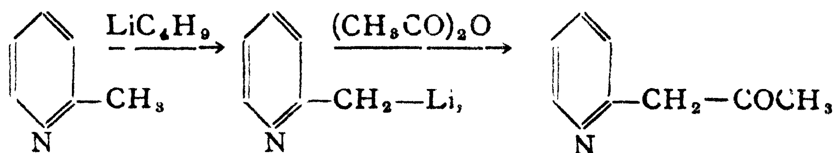
isopelletierine pelletierine

The other two alkaloids *iso-pelletierine* and *methyl-iso-pelletierine* are present in small quantities. They are simply related to each other; one is the *N*-methyl derivative of the other. They contain a ketonic group in the side-chain. The exact position of the *CO* group and the structural formulas of the molecules have been established by Hess, Meisenheimer and others. Iso-pelletierine and methyl iso-pelletierine have been assigned the following formulas :—





These structures are in full agreement with the behaviour of the alkaloids on oxidation and reduction. Isopelletierine has been synthesised by the following method :

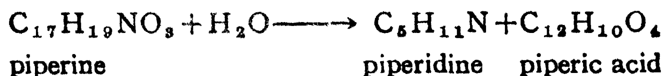


The latter on reduction with H_2 in presence of pt gives iso-pelletierine.

PEPPER ALKALOIDS :—The fruit and seeds of the species *Piper nigrum* contain an alkaloid which is called *piperine.* It is a tasteless crystalline alkaloid.

CONSTITUTION :—Piperine is a weakly basic and optically inactive compound with the molecular formula $C_{17}H_{19}O_3N$. Its structure is based on the following analytical and synthetic evidence :-

(*a*) On hydrolysis with dilute acids, it is decomposed into piperidine and piperic acid :—

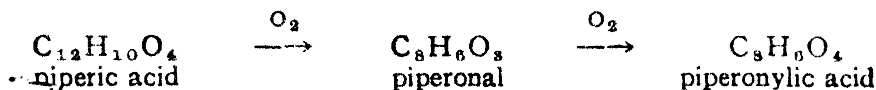


$$C_{17}H_{19}NO_3 + H_2O \longrightarrow C_5H_{11}N + C_{12}H_{10}O_4$$

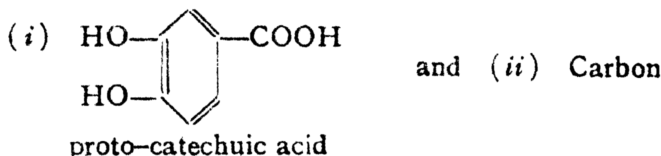
piperine piperidine piperic acid

Piperine is therefore, the piperidide of piperic acid. The nature of the nitrogen atom is also revealed by this simple reaction : it is present as the piperidine (*i.e.* the pyridine) system. That the linking of the two units is through the amide type (*CO—NH—*) is proved by the following synthesis of piperine : The chloride of piperic acid, obtained by the action of PCl_5 on the acid, is condensed with piperidine, in benzene solution to give a compound, identical with piperine (Rugheimer).

(*b*) *Structure of piperic acid.*—On oxidation with potassium permanganate, piperic acid gives piperonal, an aldehyde and finally the acid, piperonylic acid :—

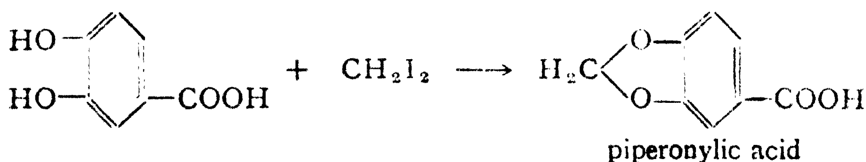


Piperonylic acid when heated with water under pressure at 220° or with hydrochloric acid at 170°, is decomposed into :—



proto–catechuic acid

Piperonylic acid must, therefore, contain the proto–catechuic acid unit. Further, that it is the methylene ether of proto-catechuic acid is indicated by the fact that on boiling with concentrated hydriodic acid, methylene iodide CH_2I_2, and proto-catechuic acid are formed. The methylene ether structure is further confirmed by a synthesis of piperonylic acid from proto-catechuic acid and methylene iodide : —



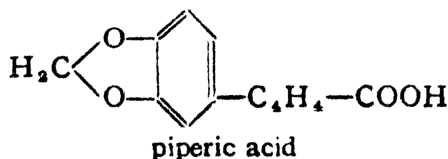
piperonylic acid

(*c*) *Relation of piperonylic acid to piperic acid* :—An examination of the molar composition of these acids :—



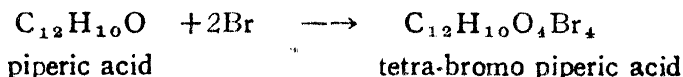
piperic acid	$C_{12}H_{10}O_4$
piperonylic acid	$C_8H_6O_4$

indicates that piperic acid differs from piperonylic acid by C_4H_4. This grouping must be so present in the molecule that on oxidation only one carboxyl group appears. The piperic acid must, therefore, contain only one side-chain on the aromatic nucleus. Hence we have :—

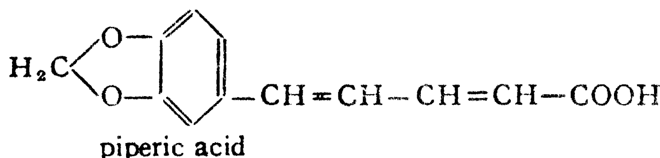


piperic acid

(The group C_4H_4 is an unsaturated one and the type of unsaturation is determined by reactions with bromine or hydrogen. When piperic acid is treated with bromine, a tetrabromo derivative is formed :—



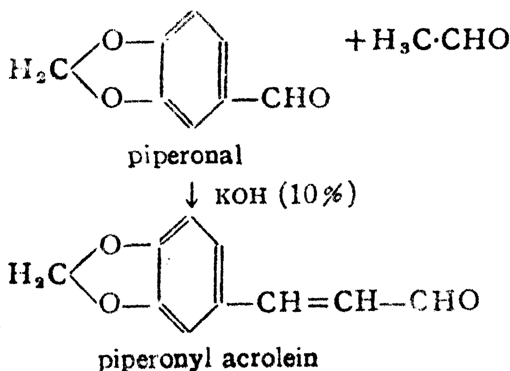
Hence, there must be either *two* double bonds or *one* triple bond in the side-chain. The formation of piperonal $C_7H_5O_2{\cdot}CHO$, and racemic acid $COOH—CHOH—CHOH—COOH$ with potassium permanganate, suggests the presence of a conjugated system of double bonds :—$HC=CH—CH=CH—(C_4H_4)$. Piperic acid must therefore be presented by :—



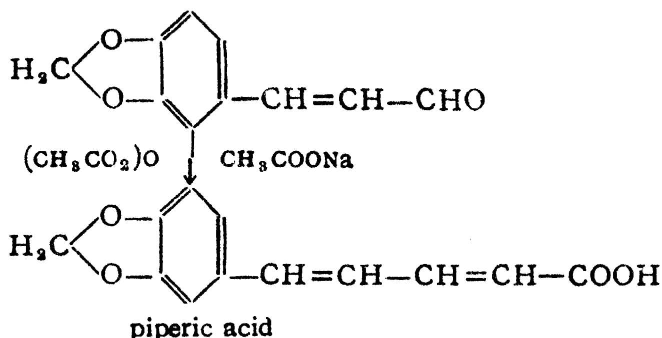
piperic acid

The above structure was confirmed by a synthesis by Ladenburg. The starting point is piperonal. The steps involved are :

(*a*) Formation of piperonyl acrolein :—

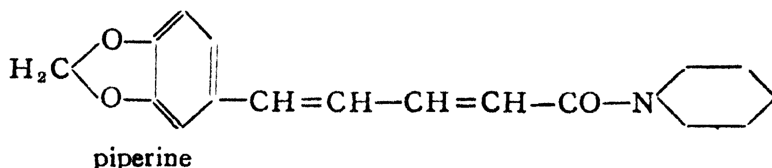


(*b*) Formation of piperic acid—(Perkin's reaction).



piperic acid

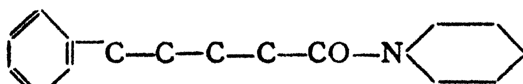
Constitution and synthesis of piperine—Piperine is the piperoylamide of piperic acid, and hence is to be represented by :



piperine

It is obtained by condensing the piperoyl chloride with piperidine in benzene solution.

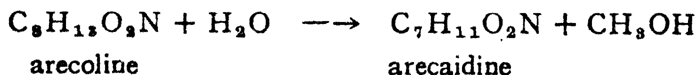
Relation between pepper-like taste and chemical constitution :—Piperine is the principal alkaloid of the pepper. However, it is now known that the sharp taste of pepper is not due to the alkaloid at all. It acts only as a local irritant and is without any physiological action. H. Staudinger has, shown that the piperine molecule may be made to undergo considerable modifications in structure without losing its characteristic taste. The essential condition is the presence of acid amide type of linking of a piperidine nucleus with a fatty aromatic acyl radical. Thus, the most effective structural unit for the production of the pepper-like taste is :—



The derivatives of δ-phenyl-*n*-valeric acid were found to possess the most pronounced pepper-like taste.

ARECA NUT ALKALOIDS.—The fruit of Areca catechu—the betel palm contains a number of alkaloids. So far, five different alkaloids have been isolated from the areca nuts. They are arecoline, arecolidine arecaidine, guvacine, and guvacoline; of these, the most important is arecoline.

ARECOLINE AND ARECAIDINE.—These are closely related to each other. On hydrolysis, arecoline is decomposed into methyl alcohol and arecaidine :—

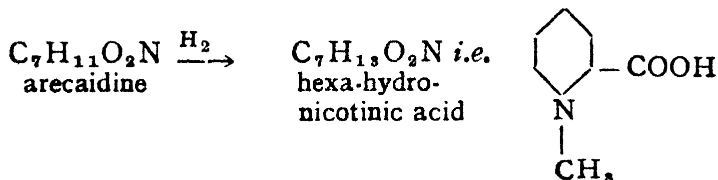


$$\underset{\text{arecoline}}{C_8H_{13}O_2N} + H_2O \longrightarrow \underset{\text{arecaidine}}{C_7H_{11}O_2N} + CH_3OH$$

Arecoline is therefore, the methyl ester of arecaidine. Arecaidine forms salts with bases and acids. Its constitution is based on the following analytical and synthetic evidence :—

(*a*) On heating arecaidine with lime, methylamine is split off, thus indicating the presence of $N-CH_3$ group in the molecule. Hydrochloric acid at 24°, eliminates a molecule of methyl chloride.

(*b*) Reduction of arecaidine with sodium and alcohol gives *N*-methyl-hexa-hydro-nicotinic acid :—

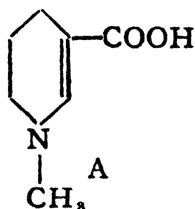


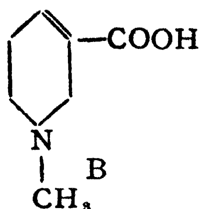
$$\underset{\text{arecaidine}}{C_7H_{11}O_2N} \xrightarrow{H_2} \underset{\text{hexa-hydro-nicotinic acid}}{C_7H_{13}O_2N}\ \textit{i.e.}$$

i.e. two atoms of hydrogen are added to form hexa-hydronicotinic acid.

These results thus indicate that arecaidine is a pyridine carboxylic derivative and contains one double bond. It is to be formulated as tetrahydro-N-methyl nicotinic acid. The exact position of the double bond is established as follows :—

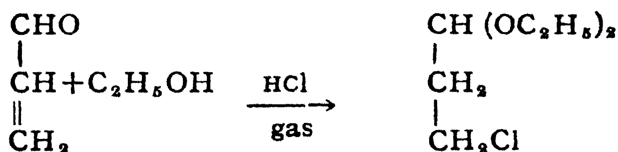
(*a*) Neither the naturally occurring nor the synthetic arecaidine is optically active, hence the double bond should be so present that the molecule should not include an asymmetric carbon atom. Hence structures A and B are only two theoretically possible ones.



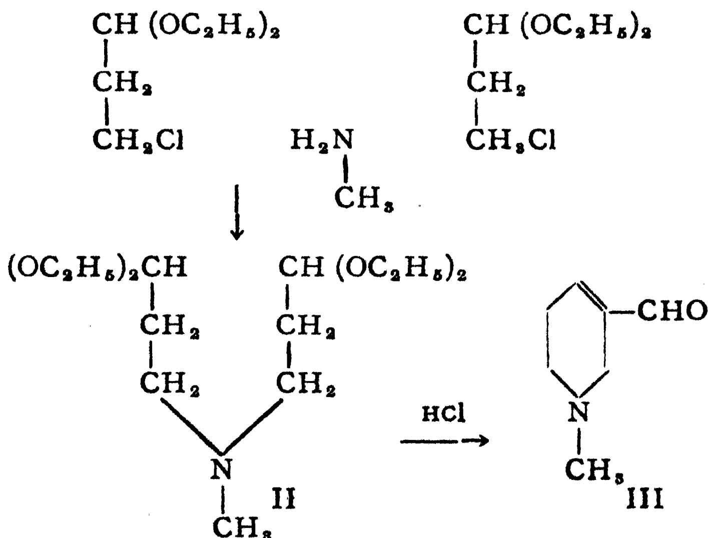


(*b*) That structure B is the correct one for arecaidine is proved by a synthesis by Wohl. The steps involved are :—

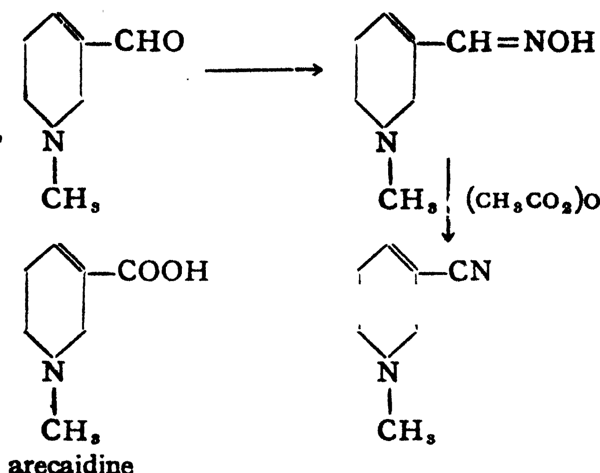
1. Acrolein is converted into the diacetal of β-chloropropionaldehyde (I).



2. The acetal (I) is condensed with methylamine to form methyl-amino-di-propionaldehyde diacetal (II), which readily suffers ring closure, when treated with cold hydrochloric acid to yield the aldehyde (III), corresponding to arecaidine :

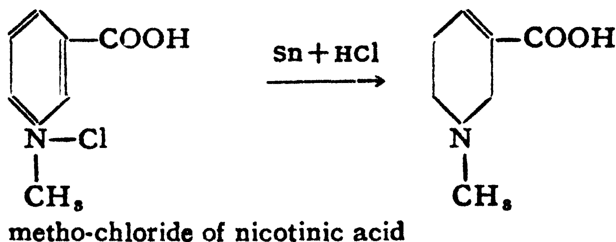


The aldehyde is then converted into the acid *i. e.* arecaidine



arecaidine

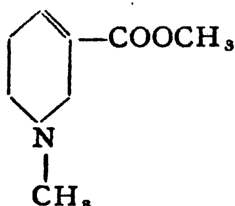
The above structure is partly confirmed by a synthesis by Jahns. The metho-chloride of nicotinic acid is reduced with tin and hydrochloric acid, when arecaidine is formed :—



metho-chloride of nicotinic acid

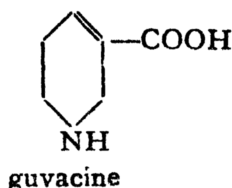
This synthesis, however, leaves open the question of the location of the double bond.

The structure of arecoline which is the methyl ester of arecaidine, is therefore, given by the formula :—

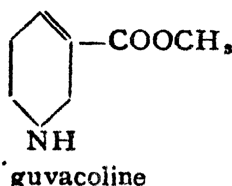


The alkaloids *guvacine* and *guvacoline* are related to each other in the same way as arecoline and arecaidine. Thus, guvacoline is the methyl ester of guvacine. Guvacine differs from arecaidine in not

having a methyl group on the nitrogen atom. The structural formulas for these alkaloids are :—



guvacine



guvacoline

Guvacine and guvacoline are also called *nor*-arecaidine and *nor*-arecoline respectively.

CASTOR BEAN ALKALOIDS :—The seeds of castor oil plant contain the alkaloid, ricinine. It was first isolated by Tuson. Its structural formula has been established by Maquenne and Spath.

Ricinine has the molecular formula $C_8H_8O_2N_2$. It gives the following reactions :—

(*a*) On distillation with zinc dust, ricinine gives pyridine :—



$$\underset{\text{ricinine}}{C_8H_8O_2N_2} \longrightarrow \underset{\text{pyridine}}{C_5H_5N}$$

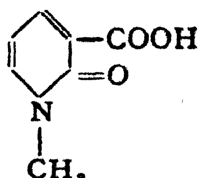
The presence of a pyridine system is thus indicated. Further, the formation by catalytic reduction of a tetra-hydro derivative, points to the presence of a di-hydrogenated pyridine.

(*b*) With alkali, ricinine gives methyl alcohol and ricininic acid with the molar composition $C_7H_6O_2N_2$. The latter, on treatment with phosphorus oxychloride and subsequent reduction, gives ricinidine, $C_7H_6ON_2$.

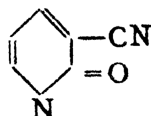


$$\underset{\text{ricininic acid}}{C_7H_6O_2N_2} \longrightarrow C_7H_5ON_2Cl \longrightarrow \underset{\text{ricinidine}}{C_7H_6ON_2}$$

The structure of ricinine is based on that of ricinidine. Ricinidine can be hydrolysed in two distinct stages. An amide of the composition $C_7H_8O_2N_2$ is first formed, which, on subsequent hydrolysis, gives an acid $C_7H_7O_3N$, and one molecule of ammonia. These results indicate that ricinidine is a nitrile. The acid $C_7H_7O_3N$ is found to be identical with synthetic 1-methyl-2-pyridone-3-carboxylic acid :—

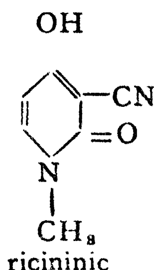


Hence, ricinidine would be represented by :-

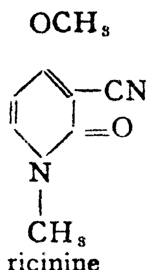


ricinidine

Ricininic acid and ricinine would then be :



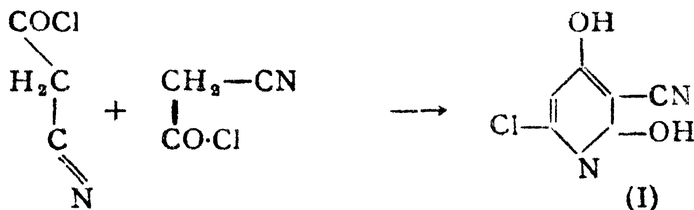
ricininic



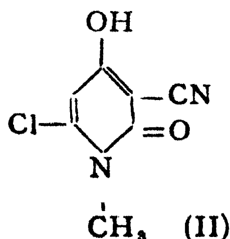
ricinine

The above structures have been confirmed by a synthesis by Spath, Schroeter and others.

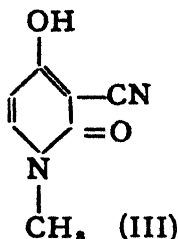
Schroeter's synthesis.—(*a*) Cyano-acetyl chloride, on standing, polymerises to 2-4 dihydroxy-6-chloro-nicotinic acid (1).

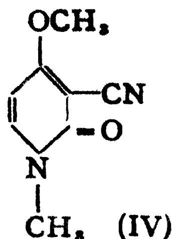


(*b*) Methylation of (I) gives the *N*-methyl 2-pyridone derivative (II), which is 6-chloro-ricininic acid.



(*c*) The 6-chloro-ricinic acid, on reduction, is converted into ricininic acid (III), which, on methylation, gives ricinine (IV).



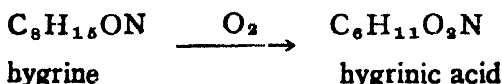


Ricinine is thus *N*-methyl-3-cyano-4-methoxy-2-pyridone. It is weakly basic and intensely bitter. It is optically inactive.

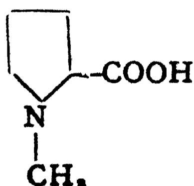
ALKALOIDS WITH A PYRROLE NUCLEUS

The coca leaves contain in addition to the cocaine alkaloids, two important pyrrolidine alkaloids, hygrine and cusco-hygrine. Hygrine is a liquid and it is optically active.

STRUCTURE OF HYGRINE.—The problem of its structure was completely solved by Liebermann. The molar composition is $C_8H_{15}ON$. It forms an oxime with hydroxylamine; hence, the oxygen is present as a carbonyl group. On oxidation with chromic acid in H_2SO_4, hygrine yields an acid with the composition $C_6H_{11}O_2N$:—

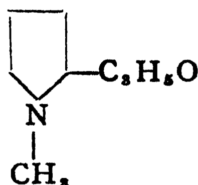


Hygrinic acid is a mono-basic acid and on heating loses carbon dioxide and is changed into *N*-methyl pyrrolidine. Hygrinic acid, therefore, must be a carboxylic derivative of *N*-methyl-pyrrolidine. The ease of decarboxylation suggests that the carboxyl group is in α-position to the nitrogen atom. Hence, hygrinic acid would be formulated as:—

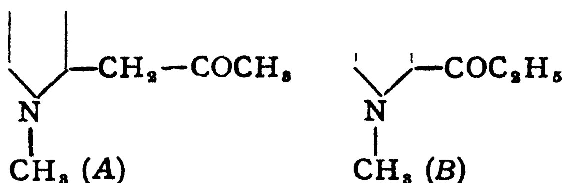


Willstatter has confirmed the above structure for hygrinic acid by an elegant synthesis. Now, hygrinic acid is formed from hygrine

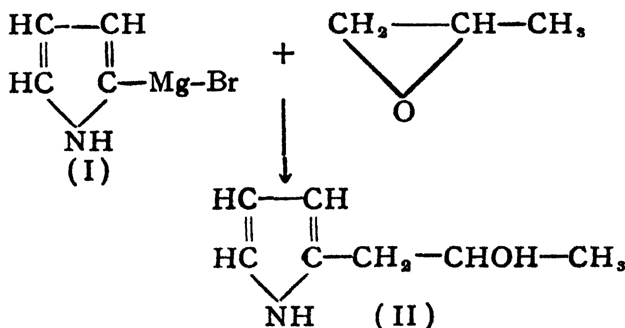
by oxidation. Hence, the latter must be an ∝-derivative of *N*-methyl pyrrolidine *i. e.* :



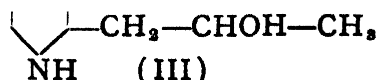
But hygrine is a ketone and the formation of hygrinic acid (C_6 from hygrine C_8) further suggests that it may be formulated either as *A* or as *B* :



Synthesis of hygrine :—The choice between the two formulae (*A*) and (*B*) is made by a synthesis due to Hess. The important steps in the synthesis can be formulated as follows:—(*i*) Pyrryl-magnesium bromide (I) is treated with propylene oxide and subsequently hydrolysed to give ∝-pyrryl-propanol (II):—

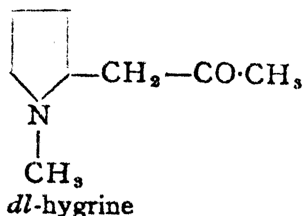


(*ii*) On catalytic hydrogenation, (II) gives the corresponding pyrrolidine drivative (III):—



(*iii*) The pyrrolidyl-propanol compound is heated with formadehyde when methylation of *NH* group and oxidation of the *CHOH*

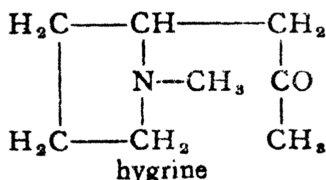
group takes place, simultaneously. This is the Eschweiler reaction. The product of the reaction is a compound identical with *dl*-hygrine hence it would be:



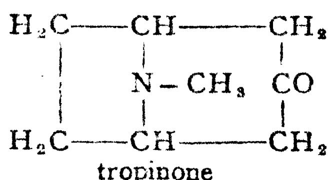
dl-hygrine

Thus the above synthesis definitely establishes that hygrine has the structure A.

The close association of hygrine and the alkaloids of the cocaine group suggests a relationship between their structures. Hygrine and tropinone—the basic framework of the cocaine alkaloids, appear thus to be structurally related:—

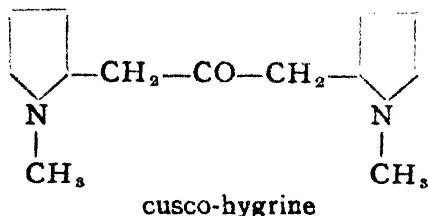


hygrine



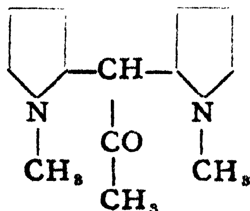
tropinone

CUSCO-HYGRINE:—Its composition is $C_{13}H_{24}ON$. It is very closely related to hygrine; alcoholic alkali decomposes it into hygrine, while oxidation converts it into hygrinic acid. The following formula has been proposed for cusco-hygrine by Liebermann:—



cusco-hygrine

An alternative formula has been advanced by Hess:—

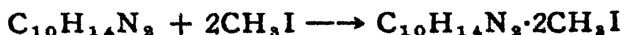


But Hess himself has subsequently advanced the strongest evidence in favour of Liebermann's formula. The evidence is based on the results of exhaustive methylation of the α-and β-forms of dihydro-cusco-hygrine obtained from cusco-hygrine with Na and alcohol. The degradation of the mixture by Hofmann's exhaustive methylation, (the product being hydrogenated at each step of the degradation) gave rise to *n*-undecane and *n*-undecan-6-ol. The Hess formula cannot give rise to these products. Finally a syhthesis confirming the Liebermann's formula has been achieved. It consists in the dry distillation of the salt of (N-methyl-α-pyryl)-acetic acid and in the subsequent catalytic hydrogenation of the ketone formed.

TOBACCO ALKALOIDS:—The leaves of tobacco contain a number of closely related alkaloids. The chief constituent is ***nicotine.*** It is present in the plant as the salt of malic and citric acids. It is an alkaloid of great commercial importance. The minor alkaloids associated with it in the plant are: iso-nicotine and nicotoine. The powdered leaves and stems of tobacco are extracted with water which dissolves the combined alkaloids. The free alkaloid nicotine is then obtained by treatment with alkali and subsequent steam distillation. The crude base is further purified in the form of its oxalate. It is a liquid (b.p. 270°). It is a powerful poison; in dilute solutions, it is used extensively as an insecticide in agriculture. It is *l*-rotatory, but its salts are *d*-rotatory.

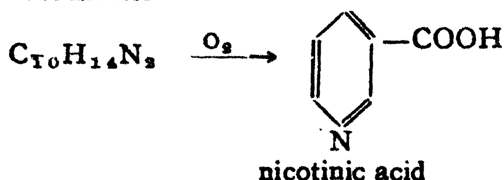
CONSTITUTION OF NICOTINE:—Nicotine is a strongly basic liquid alkaloid with the molar composition $C_{10}H_{14}N_2$. Its structure is based on the results of degradative methods like oxidation and on direct synthesis.

Nature of the nitrogen atoms:—The nitrogen atoms of the alkaloid are tertiary as one molecule of nicotine combines with two molecules of methyl iodide.



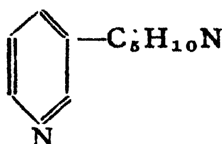
$$C_{10}H_{14}N_2 + 2CH_3I \longrightarrow C_{10}H_{14}N_2{\cdot}2CH_3I$$

On oxidation with chromic acid in sulphuric acid or with HNO_3 nicotine gives nicotinic acid



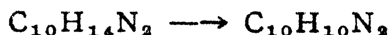
nicotinic acid

Nicotine, thus, is a β-pyridyl derivative. The formula for nicotine may be written as :—



The presence of the pyridine nucleus is further confirmed by the formation of a hexa-hydro derivative, on reduction with sodium and alcohol. Thus one of the two nitrogen atoms is present as a pyridine system.

On dehydrogenation with silver oxide, nicotine yields nicotyrine.



$$C_{10}H_{14}N_2 \longrightarrow C_{10}H_{10}N_2$$

i.e. 4 H atoms are eliminated simultaneously, which suggests the presence of a five membered ring *i. e.* pyrrolidine system in the molecule.

Nature of the side-chain.—The side-chain, $C_5H_{10}N$ has the same composition as the piperidyl group and for some time it was assumed that nicotine was piperidyl-pyridine, the synthetic evidence of Blau that hexahydronicotine obtained by the reduction of nicotine with Na and amyl alcohol, is not identical with dipiperidyl, rules out the piperidyl-pyridine structure for nicotine.

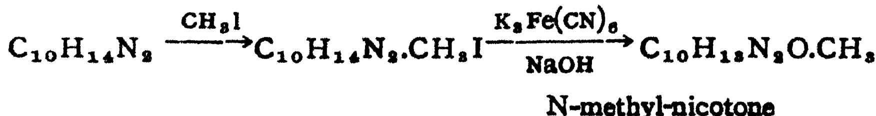
A few other reactions of nicotine are :—

(*a*) nicotine, on heating with HI at 200–300°, gives CH_3I.

(*b*) nicotine zinci-chloride ($C_{10}H_{14}N_2.ZnCl_2.2HCl.H_2O$) on distillation with lime, gives pyridine, methylamine and pyrrole.

These results indicate the presence of (*i*) a pyridine unit, (*ii*) a pyrrole unit and (*iii*) N—CH_3 group in the nicotine molecule.

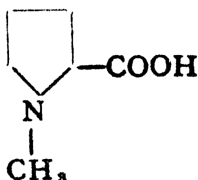
The presence of N-methyl-pyrrolidine nucleus in clearly indicated by the conversion of nicotine into hygrinic acid.



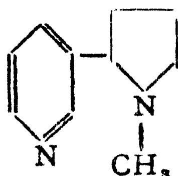
$$C_{10}H_{14}N_2 \xrightarrow{CH_3I} C_{10}H_{14}N_2.CH_3I \xrightarrow[NaOH]{K_3Fe(CN)_6} C_{10}H_{12}N_2O.CH_3$$

N-methyl-nicotone

The latter on oxidation with $Na_2Cr_2O_7$ and H_2SO_4 gives 1-hygrinic acid.



Hence nicotine contains (a) pyridine nucleus and (b) N–methyl pyrrolidine nucleus; and as nicotinic acid (β-derivative) and hygrinic acid (*2* derivative) are formed. The structure for nicotine must be:



Pinner's researches : Pinner elucidated the exact nature of the side chain and the final structure of nicotine in a different way. He found that nicotine with bromine in acetic acid gives a dibromo derivative dibromocotinine $C_{10}H_{10}N_2OBr_2$; with bromine in hydro–bromic acid, on the other hand, the dibromo derivative, dibromo-ticonine $C_{10}H_8N_2O_2Br_2$ is formed.

Dibromo-cotinine when heated with a mixture of sulphurous and sulphuric acids at 130-140°, is decomposed into :—

(*a*) methyl pyridyl ketone : —CO—CH_3

N

(*b*) oxalic acid and (*c*) methylamine.

Dibromo-ticonine, on heating with barium hydroxide, in a sealed tube at 100°, gives :

(*a*) nicotine acid, (*b*) malonic acid and (*c*) methylamine.

These results of degradation suggest that nicotine molecule must contain the following structural units :—

(i) —C—C (present in methyl ketone of pyridine)

N

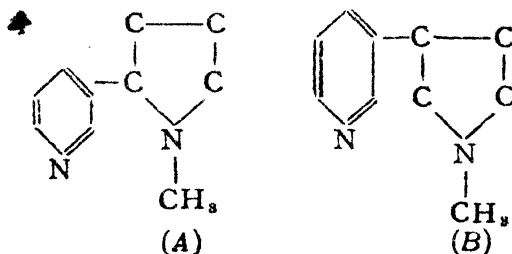
(*ii*) C—C—C (present in malonic acid)

(*iii*) N—CH_3 (present in methylamine)

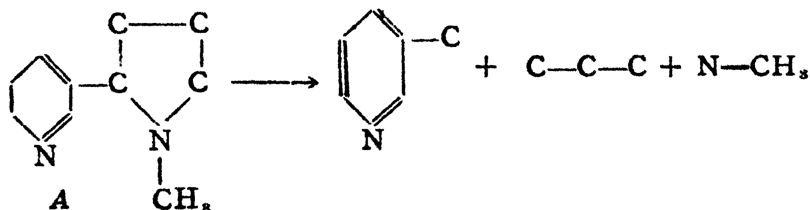
The C—C system found in oxalic acid may be derived from the C—C—C system.

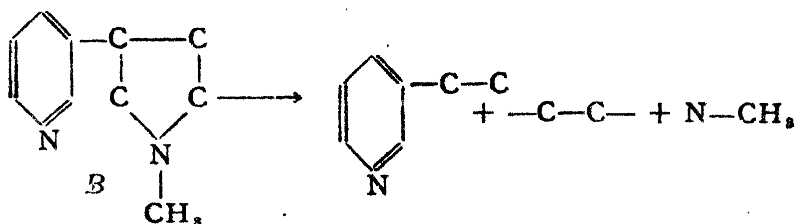
Now, nicotine on oxidation, gives nicotinic acid. Hence, the possibility of the four carbon atoms (one is present as methyl group) being present as more than one side-chain is excluded. The four carbon atoms may form a closed-chain system with the N-CH_3 group, i.e. the side-chain is probably N-methyl pyrrole system. The presence of a hydrogenated pyrrole ring system is indicated by the fact that four hydrogen atoms are lost simultaneously on dehydrogenation of nicotine with silver oxide (see p. 367). The results of distillation with lime, also, indicate the presence of a pyrrole nucleus.

The mode of linking of the pyrrole nucleus.— The pyrrole nucleus may be attached to the pyridine nucleus in the β-position in two ways as in (*A*) or (*B*) as indicated below.

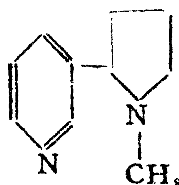


The formation of malonic acid with the three-carbon system as one of the products of decomposition shows that the carbon atoms of the four carbon chain, *i.e.* the pyrrole nucleus must be linked through the α-position to the pyridine nucleus in *β*-position (of the *N* atom of pyridine) as in formula (*A*). The decomposition of the two structures may be schematically represented as below :—



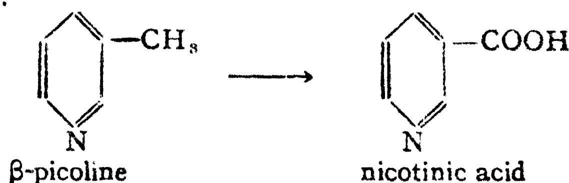


But with formula (*B*), the formation of malonic acid (*C—C—C* system) is not possible. Hence, nicotine must be represented by :

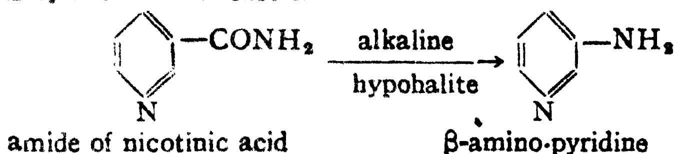


Synthesis of nicotine.—Pictet and Rotschy achieved the first complete synthesis of nicotine. The essential steps in this synthesis are :—

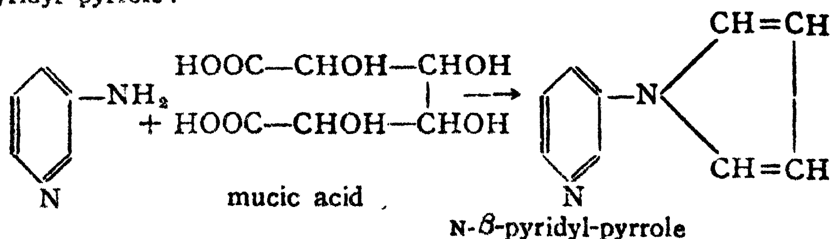
(*a*) Synthesis of β-amino-pyridine : β-picoline is oxidised to nicotinic acid :—



The amide of nicotinic acid is then converted into β-amino pyridine by Hofmann's reaction :—

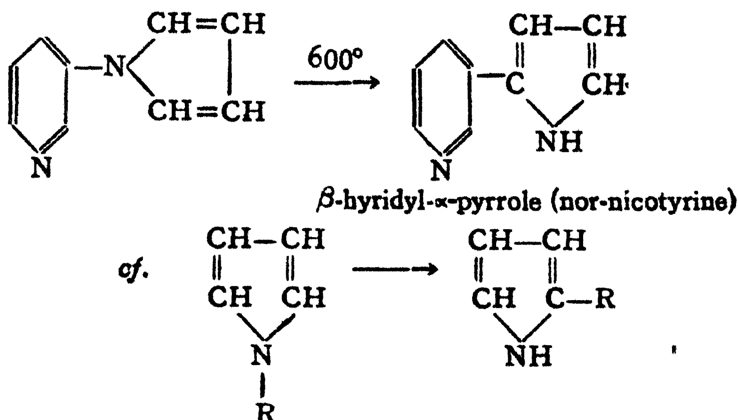


(*b*) β-Amino pyridine is heated with mucic acid to form *N*-β pyridyl-pyrrole :—

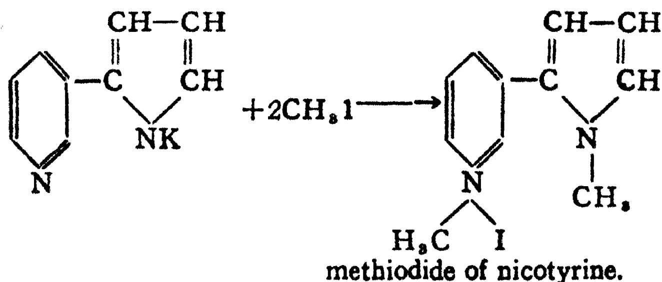


(*cf.* the synthesis of pyrrole from the NH_4-salt of mucic acid).

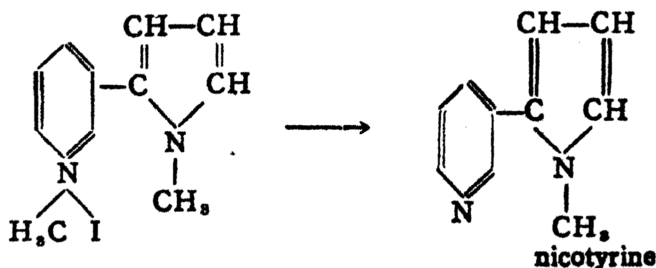
The latter, on passing through a red hot tube, is changed into a *C*–derivative *β*–pyridyl–*α*–pyrrole :—



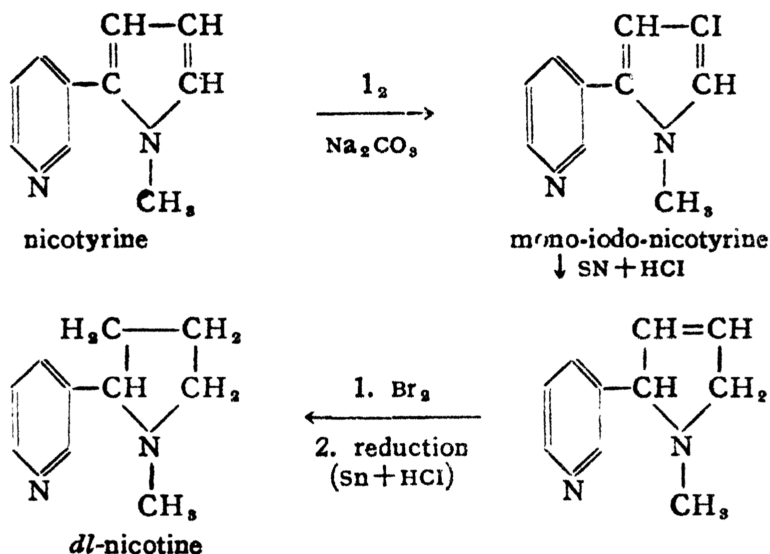
The potassium salt of this compound is treated with methyl iodide to form the methiodide of nicotyrine :—



Gentle distillation with lime gives nicotyrine. (The CH_3I molecule from the pyridine nitrogen atom is removed):—



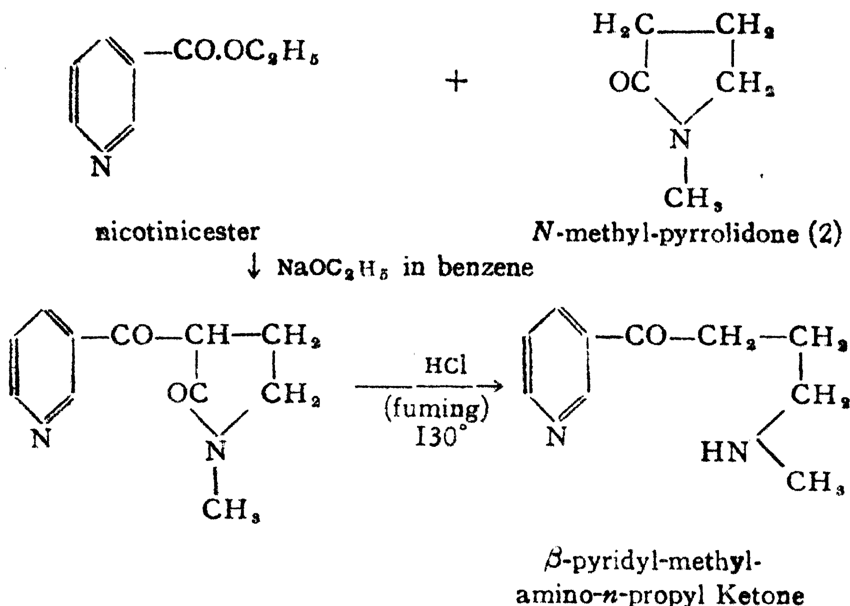
The reduction of nicotyrine to nicotine required nearly ten years of patient research. The reduction cannot be effected by any of the usual reducing agents as they will attack both the pyridine and pyrrole nuclei. It is however, carried out in an indirect way. Mono-iodo nicotyrine is first obtained by the action of I_2 in alkali, which is then reduced to dihydro-nicotyrine with tin and an acid. The latter is again brominated and the perbromide derivative is further reduced to *dl*-nicotine :—



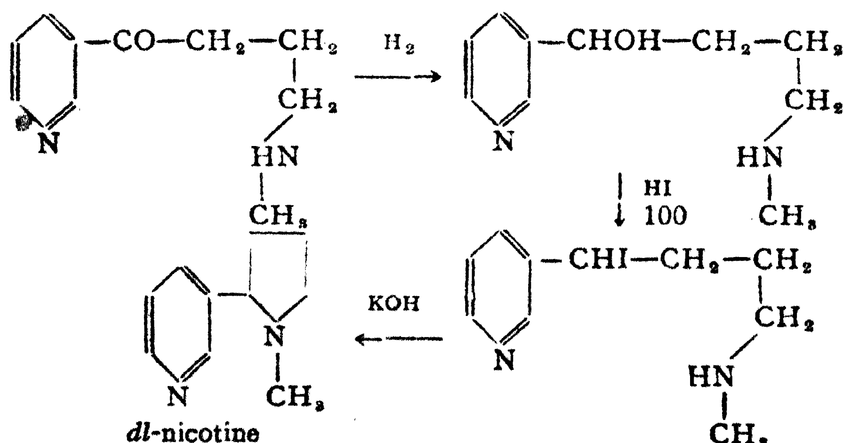
Quite recently, Spath and Kuffner have effected a direct controlled hydrogenation of nicotyrine to *dl*-nicotine by hydrogen in the presence of *Pd*-charcoal as a catalyst.

The racemic product of the synthesis was resolved by means of *d*-tartaric acid and the *l*-base so obtained was identical with the natural alkaloid.

A less drastic and less complicated but more obvious synthesis has been achieved by Spath. The starting-points are nicotinic ester and *N*-methyl pyrrolidone : the latter is obtained from succinimide by electrolytic reduction and subsequent methylation. The various steps involved are formulated below :—

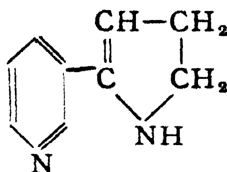


The ketone is reduced by boiling with zinc dust and alcoholic alkali or with Pd/C and H_2, and subsequently heated with hydriodic acid; the iodo derivative thus formed on treatment with aqueous alkali suffers ring closure and gives *dl*-nicotine. This synthesis leaves no doubt regarding the point of attachment of the pyrrole nucleus to the pyridine nucleus.



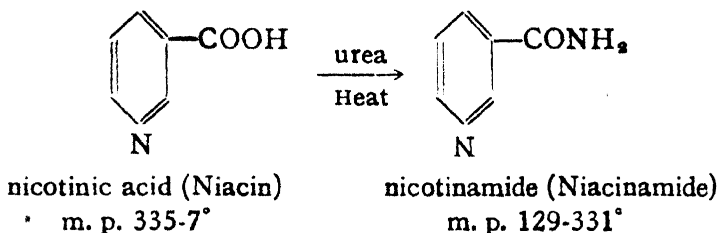
The above synthesis leaves no doubt regarding the point of attachment of pyridine and the pyrrole nuclei in the molecule.

Recently, the constituents of the smoke of tobacco have been investigated. The peculiar aroma has been ascribed to the presence of myosmine and the three sokratines. Myosmine has been assigned the following structure :—



myosmine

Derivatives of Nicotine.—Nicotinic acid (obtained by the oxidation of nicotine) and the corresponding amide are important compounds.



nicotinic acid (Niacin) m. p. 335-7°   nicotinamide (Niacinamide) m. p. 129-331°

Both are crystalline compounds; they possess an activity similar to that of vitamin B_2 complex. They find use as prophylaxis against pellagra. The amide is preferred to the acid as it does not produce any undesirable after effects.

Coramine—The diethyl amide of nicotinic acid is also an important modern drug. It resembles camphor in its physiological properties. It has thus a stimulating effect on the heart and finds use as an antidote to morphine and as a powerful heart stimulant.

Alkaloids With Condensed Pyridine and Pyrrole Systems or the solanceous alkaloids.

The most important alkaloids which belong to this class are the belladona and the coca alkaloids. Henbane and the thorn apple also contain alkaloids that contain the condensed pyridine and pyrrole systems. These alkaloids when chewed, smoked or consumed in decoction cause hallucinations.

Belladona Alkaloids—Alkaloids of the Deadly Night-shade

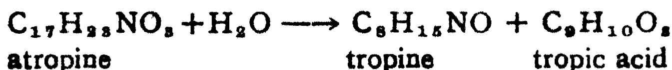
The most important alkaloid of belladona is *atropine*; It is contained in the root of deadly night-shade. It is the racemic form of *l*-hyoscyamine; the atropine of commerce is obtained by the racemisation of hyoscyamine with dilute alkali. It is used in medicine for dilating the pupil of the eye, and also in the form of a paste, for relieving local pain.

The alkaloid is extracted from either the powdered root of belladona or the plant juice datura.

The plant juice contains besides atropine, the active isomeric alkaloid hyoscyamine and scopolamine. The juice is treated with dilute alkali, when racemisation occurs; the inactive atropine is then extracted with ether and subsequently purified in the form of its sulphate or oxalate. The free base is a crystalline compound m. p. 115–116°C; it possesses a bitter taste; when warmed with H_2SO_4 and a small quantity of $K_2Cr_2O_7$, atropine develops bitter almond odour.

Structure of Atropine—The names associated with the elucidation of the chemical constitution of atropine are Ladenburg, Merling and Willstatter. The evidence is as follows :—

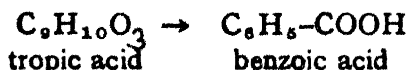
The molecular formula of atropine is $C_{17}H_{23}NO_3$. On hydrolysis with acids HCl at 130° or alkalies $Ba(OH)_2$ at 60°, atropine yields (*i*) tropine and (*ii*) tropic acid.



$$\underset{\text{atropine}}{C_{17}H_{23}NO_3} + H_2O \longrightarrow \underset{\text{tropine}}{C_8H_{15}NO} + \underset{\text{tropic acid}}{C_9H_{10}O_3}$$

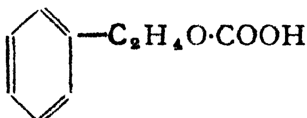
Atropine is, therefore, an ester. It is tropine-tropate. This was corroborated by Ladenburg who obtained atropine by evaporating a mixture of tropine and tropic acid in presence of hydrochloric acid. It cannot be an amide because tropine the product of hydrolysis is a tertiary base.

Tropic acid.—It is a crystalline compound (m.p. 118°). The structure of this acid is based on the following evidence :—Vigorous oxidation of tropic acid with acid potassium permanganate gives benzoic acid :—

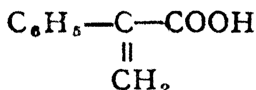


$$\underset{\text{tropic acid}}{C_9H_{10}O_3} \rightarrow \underset{\text{benzoic acid}}{C_6H_5\text{–}COOH}$$

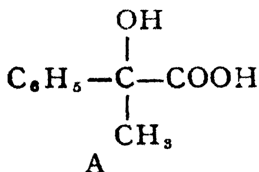
Hence, tropic acid must contain a benzene nucleus with one side-chain and as it is an acid, it must be formulated as :—

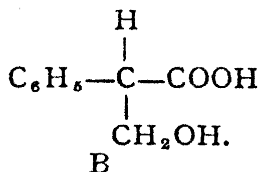


On heating with Ba $(OH)_2$, tropic acid suffers dehydration and gives atropic acid which is isomeric with cinnamic acid; atropic acid on further oxidation gives benzoic acid. Hence atropic acid must be

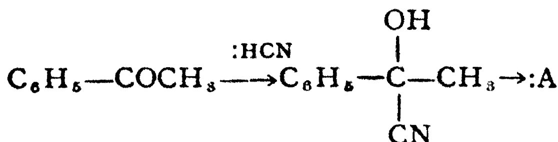


Hence tropic acid must be either A or B





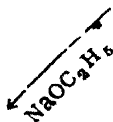
The acid A can be synthesised from aceto phenone by the cyano hydrin synthesis,

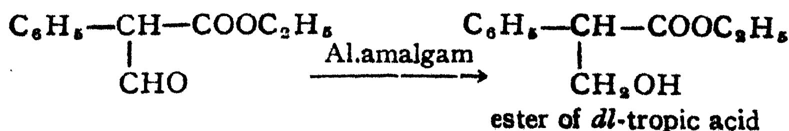


The acid is not identical with tropic acid. The latter therefore must be represented by B.

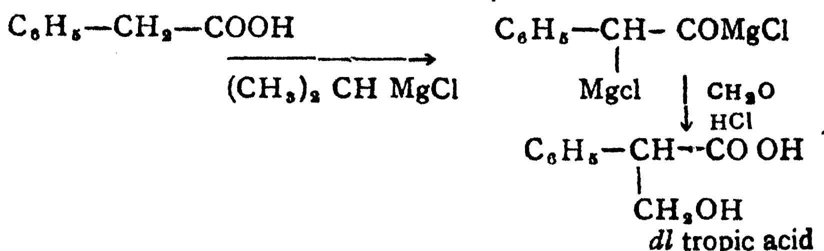
A direct synthesis of tropic acid from phenyl acetic ester constitutes an unambiguous proof for the structure assigned above (B),







there is another synthesis due to Blicke,

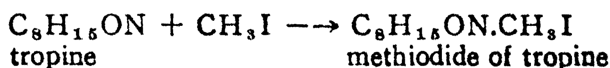


$$C_6H_5—CH_2—COOH \xrightarrow{(CH_3)_2\,CH\,MgCl} C_6H_5—\underset{MgCl}{CH}—COMgCl \xrightarrow{CH_2O,\ HCl} C_6H_5—\underset{CH_2OH}{CH}—COOH$$

dl tropic acid

Constitution of tropine:—Tropine exists in stereo-isomeric forms; it is a solid m. p. 63°. Our knowledge of the constitution of tropine is due to the researches of Willstatter and others. It is based on the following evidence:—

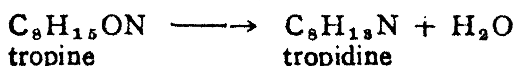
(*a*) Tropine reacts with methyl iodide to form a crystalline additive compound:—



$$\underset{\text{tropine}}{C_8H_{15}ON} + CH_3I \longrightarrow \underset{\text{methiodide of tropine}}{C_8H_{15}ON.CH_3I}$$

The nitrogen atom is therefore, tertiary. The actual presence of *N*-methyl group is indicated by the results of alkaline fusion, when methylamine is formed as one of the products of decomposition.

(*b*) By the action of dehydrating agents like sulphuric acid in glacial acetic acid, tropine is changed into tropidine:—



$$\underset{\text{tropine}}{C_8H_{15}ON} \longrightarrow \underset{\text{tropidine}}{C_8H_{13}N} + H_2O$$

Tropine, therefore must contain a secondary or tertiary alcoholic hydroxyl group.

(*c*) On gentle oxidation with chromic acid, tropine yields a ketone, tropinone. Tropinone is a crystalline compound m. p. 42°; it is optically inactive.



$$\underset{\text{tropine}}{C_8H_{15}ON} \xrightarrow{CrO_3} \underset{\text{tropinone}}{C_8H_{13}ON}$$

Hence, the alcoholic group must be *secondary* (*CHOH*) group.

(*c*) Tropinone yields both a dibenzylidene and a di-isonitroso derivative with benzaldehyde and nitrous acid respectively. It must, therefore, contain two reactive methylene groups *i. e.* $CH_2—CO—CH_2$ grouping. Hence, tropine would contain the grouping $CH_2—CHOH—CH_2$.

(*b*) Tropinone, on further oxidation gives the dibasic acid tropinic acid.

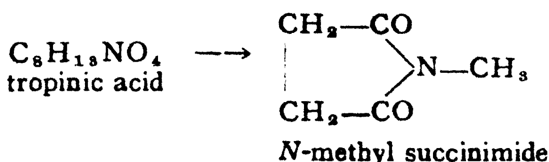


$$C_8H_{13}ON \quad O_2 \quad C_8H_{13}NO_4$$

Tropinic acid is a dibasic acid containing the same number of carbon atoms, as the ketone tropinone. Hence the latter must be a cyclic ketone.

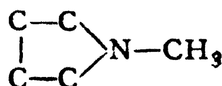
(*e*) On exhaustive methylation, tropinic acid gives a di-olefinic dibasic acid $C_5H_6(COOH)_2$ which, on reduction, gives pimelic acid. Therefore, the seven carbon atoms out of the eight, form a unbranched chain; the eighth is present as a methyl group.

(*f*) On further oxidation, tropinic acid is changed into *N*-methyl succinimide :—

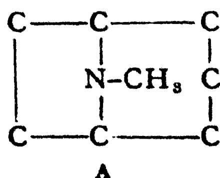


N-methyl succinimide

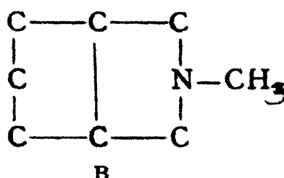
These results indicate the position of *N* and the presence of an *N*-methyl pyrrolidine system. Therefore, tropine contains the following carbon-nitrogen framework :—



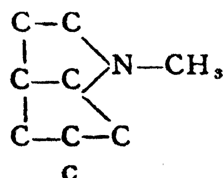
to which must be added, the system *C–CO–C*, *i. e.* (CH_2-CO-CH_2). Hence, the complete framework would be A or B or C.



A

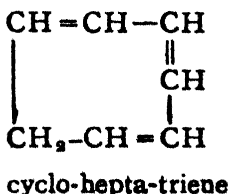


B



C

The results of exhaustive methylation, of tropidine, however clearly point to the presence of a fused pyrrolidine-piperidine system as in A. Tropidine, on exhaustive methylation, forms cyclo-hepta-triene which has the structure :—

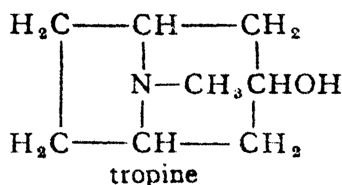


cyclo-hepta-triene

(Tropidine contained one double bond, the additional two double bonds are formed as a result of exhaustive methylation).

The formulation of the C—N—framework as in B or C would give only a cyclo-pentene derivative.

Also with bromine, tropidine gives di-bromo-pyridine and ethyl pyridine. This indicates the presence of the pyridine system. Hence tropine should be represented by :—

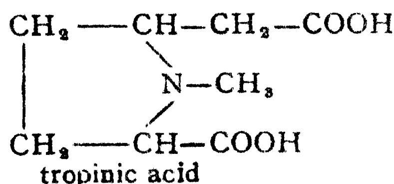


tropine

(Formulation as in B or C does not carry a pyridine ring).

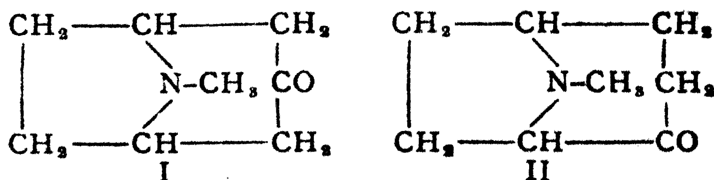
The structure of tropine may also be deduced as follows —

Tropinic acid is a *di*-carboxylic acid derived from *N*-methyl pyrrolidine; the COOH : and—CH_2—COOH may be in α or β positions; if they are present in the latter, exhaustive methylation would not give a product that is reduced to, pimelic acid. Hence the two groups are in α and α' positions. Hence tropinic acid must be :



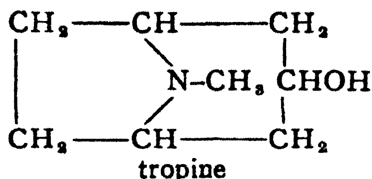
tropinic acid

this is obtained by oxidation of tropinone; tropinone and tropinic acid contain the same number of C atoms; hence tropinone must be a cyclic ketone (I or II).



But tropinone contains the system CH_2—CO—CH_2—Therefore it must be represented by structure I.

The structure of tropine, the corresponding secondary alcohol is,



tropine

Synthesis of tropine.—Willstatter, starting from suberone obtained: cyclo-hepta-triene. The latter is then converted into tropine, through a long series of reactions, which is given below :—

```
CH₂—CH₂—CH₂                      CH₂—CH=CH
|           \                    |        \
|            C=O   ——→           |         CH
|           /                    |        /
CH₂—CH₂—CH₂                      CH = CH—CH
   suberone                      cyclo-hepta-triene

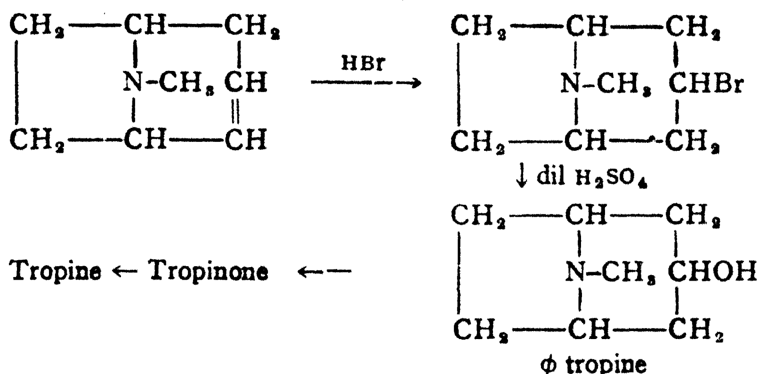
CH₂—CH=CH₂                         CH₂——CH——CH
|        \         HBr and         |    |    ||
|         CH      ————————→        |  N(CH₃)₂ CH
|        //       (CH₃)₂NH         |          |
CH = CH—CH                         CH₂——CH===CH
                                         ↓ H₂

CH₂——CH——CH₂                         CH₂——CH——CH₂
|    |    |            Br₂           |    |    |
|  N(CH₃)₂ CH₂       ←————           |  N(CH₃)₂ CH₂
|         |                          |         |
CH₂——CHBr—CHBr                       CH₂——CH===CH
     ↓ intramolecular alkylation

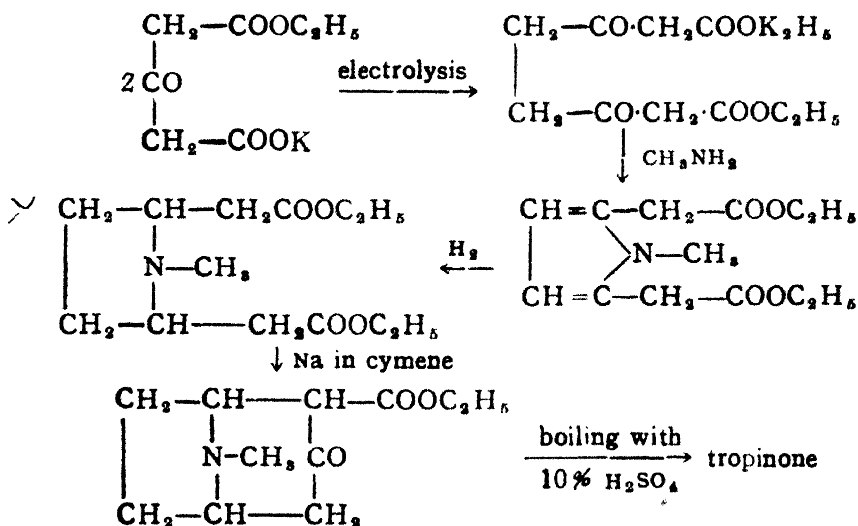
CH₂——CH——CH₂                         CH₂——CH——CH₂
|    |    |            -HBr          |    |    |
|  N(CH₃)₂ CH₂       ————————→       |  N—CH₃  CH
|   ∧Br   |            -CH₃Br        |    |    ||
CH₂——CH——CH₂                         CH₂——CH——CH
                                         tropidine
```

This synthesis is based on the alkylating action of a halogenated alkyl residue on the basic *N*–atom present in the same molecule. Such a reaction is called by Willstatter "intramolecular alkylation"; and leads to the synthesis of a cyclic base of which the *N*–atom forms a part.

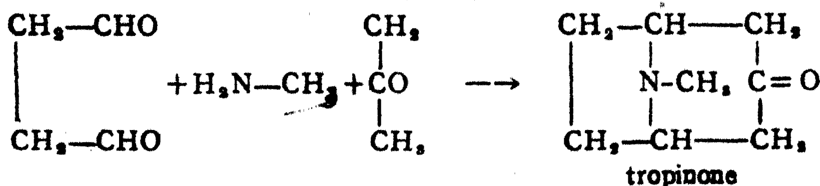
Tropidine then converted into tropine :



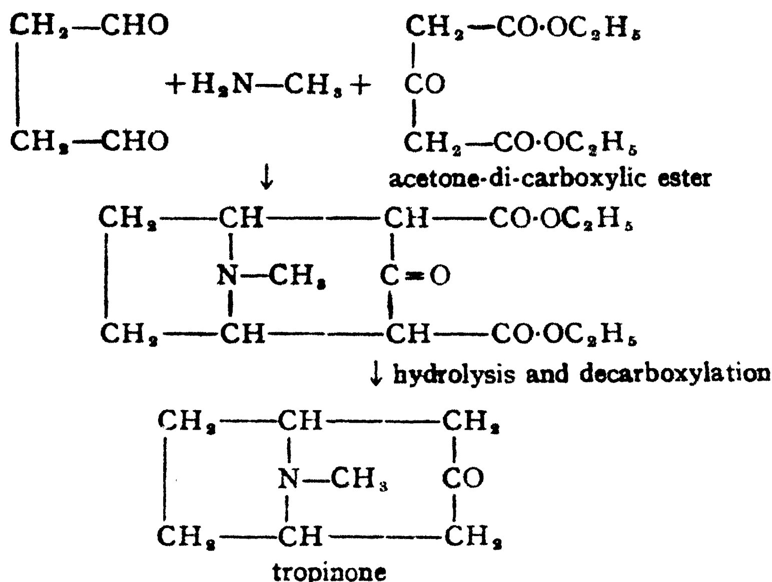
Willstatter has also reported another simple synthesis of tropinone. The starting-point is acetone-di-carboxylic-acid.



Later on, Robinson has developed a simpler and more elegant synthesis. Succinic di-aldehyde (the corresponding dioxime or the acetal) is condensed with acetone in presence of methylamine under mild alkaline conditions at ordinary temperature to form tropinone :—

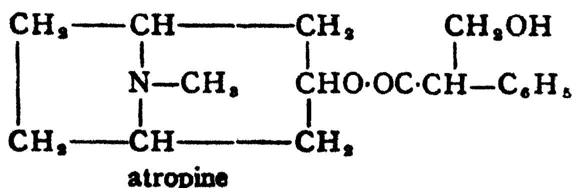


Better yields are obtained by substituting calcium salt or the ethyl ester of acetone-di-carboxylic acid in place of acetone. The corresponding di-carboxylic derivative of tropinone is obtained which is then changed into tropinone :—



Schopf and Lehmann have modified Robinson's method succin-dialdehyde, $CH_3NH_2.HCl$ and acetone-dicarboxylic acid in buffered solution at *pH* 3-11, and temperature ranging from 20-25°*C*, gives an yield of 47-86% of tropinone (when *pH* is changed to 13, tropinone dicarboxylic acid is produced). These are referred to as the simulated physiological conditions of biogenesis. On reduction with zinc dust and hydriodic acid in the cold or electrolytically, tropinone gives tropine.

Structure of atropine—Atropine has been shown to be tropine tropate. Now tropine is a tertiary base and carries no imino (*NH*) group. Hence, it is the alcoholic hydroxyl that must be involved in the ester formation. Atropine is, therefore :—



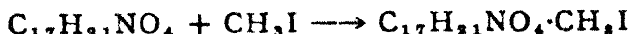
Ladenburg has confirmed this structure by preparing atropine by the evaporation of a mixture of tropic acid, and tropine in HCl.

COCA ALKALOIDS—The leaves of the shrub *Erythroxylon Coca* contain a number of closely related alkaloids called the Coca alkaloids. They include ecgonine, cocain, benzoyl-ecgonine, tropa cocaine, cinnamoyl cocaine etc. The shrub is grown in Java, Peru.

Cocaine is the chief and most important constituent of the coca alkaloids. It is manufactured as follows: all the alkaloids present in the leaves are hydrolysed to *l*-ecgonine, which is then benzoylated with $(C_6H_5CO)_2O$, and the benzoyl ecgonine is then esterified with CH_3OH and HCl to cocaine; also ecgonine is converted into cocaine in one operation, by heating it with methyl iodide and benzoic anhydride under pressure. In this way, other therapeutically unimportant congeners of cocaine are all converted into useful cocaine. Cocaine can also be directly extracted from the leaves with high boiling pertoleum. It is a crystalline compound (m. p. 98°). It is strongly basic and forms crystalline salts; the chloride is the most common. It is extensively used in medicine as a local anæsthetic for deadening pain in dental and opthalmic surgery.

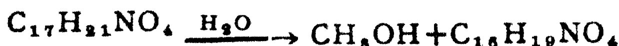
CONSTITUTION OF COCAINE—The molecular composition of cocaine is $C_{17}H_{21}O_4N$.

(1) *Nature of nitrogen atom.*—With methyl iodide, cocaine gives a crystalline methiodide showing the presence of a *tertiary* nitrogen atom.



$$C_{17}H_{21}NO_4 + CH_3I \longrightarrow C_{17}H_{21}NO_4{\cdot}CH_3I$$

(2) *Nature of oxygen atom.*—On boiling with water, cocaine is hydrolysed to methanol and benzoyl ecgonine.



$$C_{17}H_{21}NO_4 \xrightarrow{H_2O} CH_3OH + \underset{\text{benzoyl-ecgonine}}{C_{16}H_{19}NO_4}$$

Therefore cocaine is the methyl ester of benzoyl ecgonine. Benzoyl-ecgonine is further hydrolysed to benzoic acid and ecgonine.



$$\underset{\text{benzoyl-ecgonine}}{C_{16}H_{19}NO_4} \xrightarrow{H_2O} \underset{\text{ecgonine}}{C_9H_{15}O_3N} + C_6H_5.COOH$$

Also with more powerful hydrolysis with acids or alkalis, cocaine is directly changed into methanol, benzoic acid and ecgonine. Ecgonine is a crystalline compound m. p. 198; on heating with

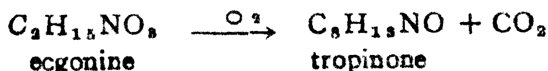
alkali, it is changed into iso-ecgonine. Its structure is based on the following evidence

(*a*) With methyl iodide, ecgonine forms the crystalline additive compound $C_9H_{15}O_5N\ CH_3I$. Hence, it is a *tertiary* base.

(*b*) It can be readily esterified and it forms salts with alkalies. The presence of a carboxyl group is thus, indicated.

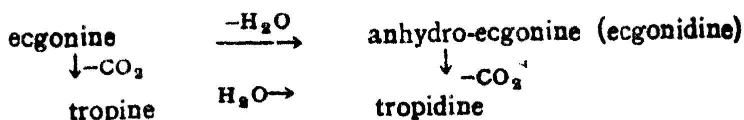
(*c*) It reacts with acid chlorides and anhydrides to form acyl derivatives: this indicates the presence of OH group. The acyl derivatives can be further esterified. This confirms that ecgonine is both an alcohol and an acid. Hence it follows that cocaine is the diester; the COOH group is esterified with CH_3OH and the alcoholic group by the benzoic acid.

(*d*) On gentle oxidation with CrO_3 in acetic acid it is converted into the ketone, tropinone with simultaneous decarboxylation :—



These results show that ecgonine must contain (*i*) *CHOH* grouping which yields the carbonyl group on oxidation and (*ii*) the carbon-nitrogen skeleton as in tropinone.

Lastly, ecgonine, when dehydrated with sulphuric acid in glacial acetic acid, gives anhydro-ecgonine $C_9H_{13}ON_2$. The latter, on heating to 280° in the presence of hydrochloric acid, loses carbon dioxide and is converted into tropidine; but tropidine is a dehydration product of tropine. The above inter-relationships can be represented as below :—



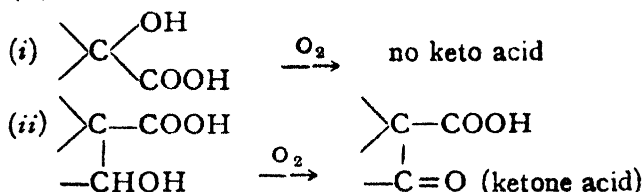
Hence, it follows that ecgonine is a *carboxylic* derivative of tropine. This is in agreement with the behaviour of ecgonine on oxidation, when tropinone and CO_2 are formed. A comparison of the molecular composition of tropine ($C_8H_{15}NO$) and ecgonine ($C_9H_{15}NO_3$) also reveals the same relationship between them.

The relative positions of COOH and OH in the molecule.—The position of the hydroxyl group is the same as in tropine because

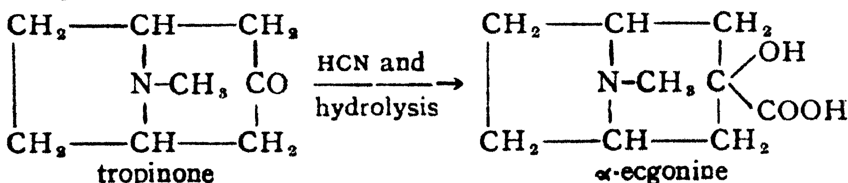
ecgonine, on oxidation gives tropinone. The position of the carboxyl group was settled by the following considerations—

(*a*) Ecgonine is converted into ecgonidine which is an unsaturated acid; the latter is then decarboxylated to tropidine; this behaviour is typical of a β-hydroxy acid.

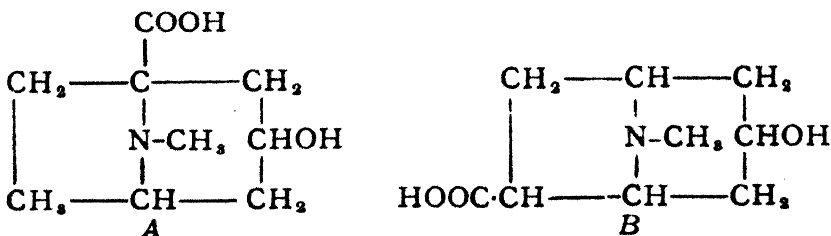
(*b*) Also, Willstatter, has reported that the oxidation of ecgonine proceeds through the formation of an intermediate keto-acid which readily loses carbon dioxide. These results definitely exclude the possibility that the hydroxyl and carboxyl groups are on the same carbon atom as in (*i*), but suggest that the OH is β to COOH as in (*ii*):



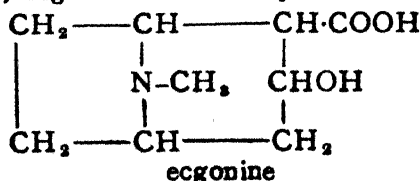
Lastly, the hydroxy acid, obtained from tropinone by cyanhydrin synthesis, is not identical with ecgonine. It is known as α-ecgonine and has the α-hydroxy acid structure :—



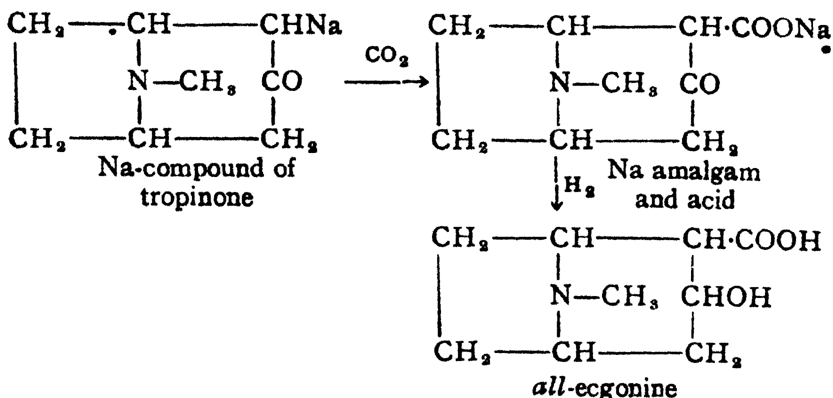
(*c*) The possibility that the COOH group may be present as in A or B *i. e* γ or δ positions is also ruled out because, these formulations do not admit of the formation of an unstable keto acid.



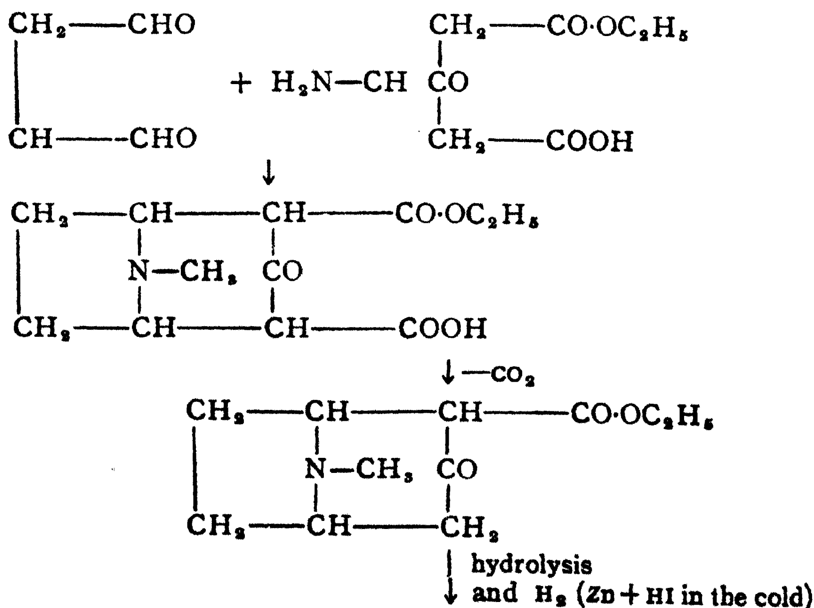
Hence, ecgonine must be represented by :—

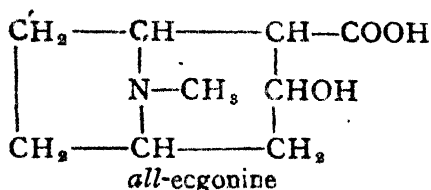


Confirmation by a synthesis.—The sodium compound of tropinone is suspended in ether at ordinary temperature and treated with carbon dioxide when a keto-acid is formed. On reduction, the latter is converted into *dl* ecgonine :—

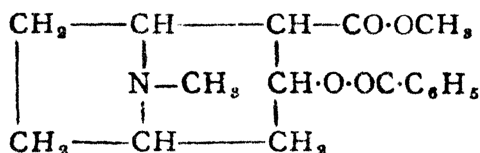


Another synthesis (Robinson) consists in the condensation of succinic di-aldehyde, acetone di-carboxylic mono-ethyl-ester and methlylyamine to form a compound which on de-carboxylation gives tropinone carboxylic ester. The latter on hydrolysis and reduction gives *dl*-ecgonine.





Structure of cocaine.—Cocaine is the methyl ester of benzoyl-ecgonine. Hence, it is :—



It can be synthesised by heating ecgonine with benzoic anhydride and subsequent esterification of the benzoyl ecgonine with methyl alcohol and an acid. A direct synthesis of *dl*-cocaine has also been achieved. Tropinone-carboxylic-methyl ester, obtained by the condensation of succinic di-aldehyde, methyl-amine and acetone di-carboxylic mono-methyl ester (see above), is reduced and subsequently benzoylated.

Alkaloids with Quinoline System
Cinchona Alkaloids

The bark, leaves etc. of the species of Cinchona and Remijia trees contain many alkaloids which are closely related to one another. The more important and typical are *cinchonine* and *quinine*. They are present in the plant bark as esters in combination with quinic and quinotannic (cincho-tannic) acids, Quinine is used extensively as a febrifuge and as an anti-malarial in the form of sulphate, chloride. or bromide. It is isolated from the bark as follows :—

The finely powdered bark is extracted several times with dil. H_2SO_4. All the alkaloids present go into soution as sulphates; the alkaloids are then precipitated with NH_4OH; the mixture of alkaloids is then dissolved in alcohol and reprecipitated as sulphates and separated by fractional crystallisation; quinine sulphate is the least soluble and hence can be completely separated from the mixture. Pure quinine is then obtained by the action of ammonia on the sulphate. Quinine is a solid m. p. 173°; it is sparingly soluble in alcohol or ether. The sulphate is the most common salt of quinine.

Constitution of quinine.—Its molecular composition is $C_{20}H_{24}N_2O_2$ and its structural formula is based on the following analytical evidence.

(*a*) With CH_3I, quinine forms a crystalline di-methiodide.

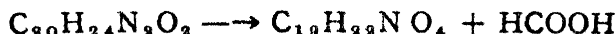


$$C_{20}H_{24}N_2O_2 + 2CH_3I \longrightarrow C_{20}H_{24}N_2O_2.2CH_3I$$

∴ Both the nitrogen atoms are tertiary.

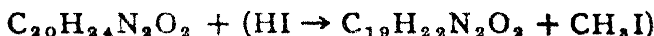
(*b*) Quinine takes up one mole of H_2 or Br_2 or HCl or HBr under suitable conditions. Hence an ethylenic double bond is indicated.

(*c*) On controlled oxidation with-$KMnO_4$, quinine gives quite fine a mono carboxylic acid derivative and formic acid.



$$C_{20}H_{24}N_2O_2 \longrightarrow C_{19}H_{22}NO_4 + HCOOH$$

∴ a vinyl group ($-CH = CH_2$) is indicated. The *Zeisel* determination shows the presence of a methoxy group :



$$C_{20}H_{24}N_2O_2 + (HI \rightarrow C_{19}H_{22}N_2O_2 + CH_3I)$$

(*d*) With acetic anhydride, quinine gives a crystalline mono-acetyl derivative. This indicates the presence of a hydroxyl group.



$$C_{20}H_{24}N_2O_2 \xrightarrow{(CH_3CO)_2O} C_{20}H_{23}N_2O_2{\cdot}COCH_3$$

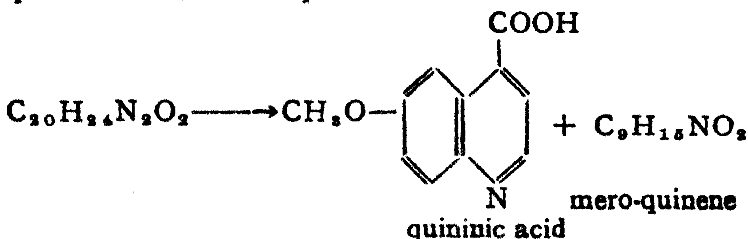
(*e*) On mild oxidation, with quinine forms a ketone quininone. Hence the alcoholic group must be a secondary one.



$$C_{20}H_{24}N_2O_2 \xrightarrow{O_2} \underset{\text{quininone}}{C_{20}H_{22}N_2O_2}$$

On fusion with KOH, quinine gives 6-methoxy-quinoline thus revealing the presence of a quinoline system.

(*f*) On vigorous oxidation with chromic acid, quinine yields quininic acid and meroquinene.



These results show that quinine is built up of a quinoline nucleus carrying a side-chain in position *four*, which ultimately appears as mero-quinene on oxidation.

Structure of mero-quinene—It has the molecular composition $C_9H_{15}NO_2$ and gives the following reactions :

(*a*) It forms a mono-sodium salt and can also be esterified ; thus the presence of a COOH group is indicated.

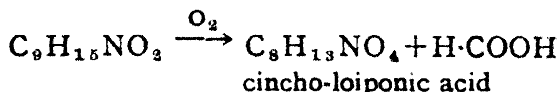
(*b*) On catalytic hydrogenation, mero-quinene takes up one mole of H_2, which establishes the presence of an ethylenic double bond. (The ethylenic double bond in quinine is present in the mero-quinene part).



$$C_9H_{15}NO_2 \xrightarrow{H_2} C_9H_{17}NO_2$$

(*c*) Mero-quinene can be acetylated, alkylated or nitrosated under suitable conditions ; this suggests the presence of a *NH* grouping.

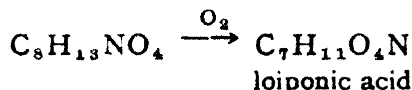
(*d*) On oxidation with potassium permanganate and H_2SO_4 in the cold, mero-quinene is converted into (*i*) cincho-loiponic acid and (*ii*) formic acid.



$$C_9H_{15}NO_2 \xrightarrow{O_2} \underset{\text{cincho-loiponic acid}}{C_8H_{13}NO_4} + H{\cdot}COOH$$

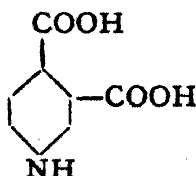
The formation of formic acid, indicates the presence of a vinyl group ($—CH=CH_2$).

Cincholoiponic acid on further oxidation with aqueous potassium permanganate, gives loiponic acid.

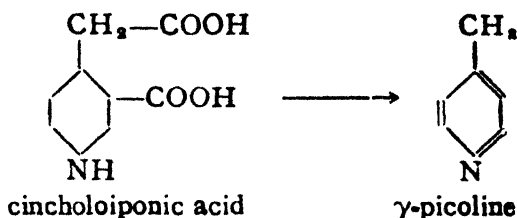


$$C_8H_{13}NO_4 \xrightarrow{O_2} \underset{\text{loiponic acid}}{C_7H_{11}O_4N}$$

these results suggest that cincho-loiponic acid is the higher homologue of loiponic acid. Now loiponic acid on heating with alkali, is converted into hexahydro-cinchomeronic acid ; this involves merely an isomeric change; probably loiponic acid is a labile form of hexahydro-cinchomeronic acid. Hence loiponic acid is



Cincho-loiponic acid is the higher homologue of loiponic acid. That the additional CH_2 group is in position 4, is indicated by the conversion of cincho-loiponic acid into γ-picoline, by the action of hot concentrated sulphuric acid (de-carboxylation and de-hydrogenation are effected). at 250–260°



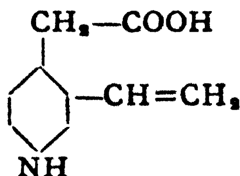
cincholoiponic acid γ-picoline

Cincholoiponic acid is formed from mero-quinene by oxidation. Mero-quinene, therefore must contain a piperidine nucleus with two side-chains in positions 3 and 4. One of these side-chains must be the vinyl group ($—CH=CH_2$), which on oxidation, would give formic acid. The position of the vinyl group would be the same as where the carboxyl group would appear :—



$$—CH=CH_2 \longrightarrow —COOH + H.COOH$$

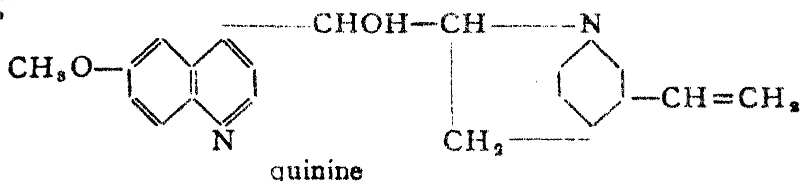
That this is in position 3, is indicated by the formation of 3-ethyl-4-methyl-pyridine from mero-quinene, on heating with a solution of $HgCl_2$ in hydrochloric acid at 250°C. The other side-chain is in position 4 and as mero quinene is a carboxylic acid, this side-chain must carry the carboxyl group. Hence mero-quinene would be best represented by :—



Mero-quinene is formed by cleavage of the second half and contains an imino nitrogen (NH) group, while quinine contains only tertiary nitrogen atoms; and as the presence of N-methyl groups is not indicated, it is obvious that as the nitrogen atom is tertiary, it must form the part of a condensed ring system. The oxidation of the quinine molecule to form mero-quinene involves oxidative degradation which leads to the production of carboxyl and imino

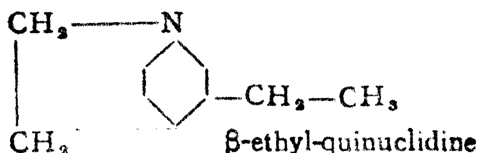
groups, and hence the carboxyl and NH groups of mero-quinene are due to the fission of a carbon nitrogen linkage.

Hence the quinoline nucleus in the quinine molecule is linked in position 4 and through a secondary alcoholic group to the second half as below :



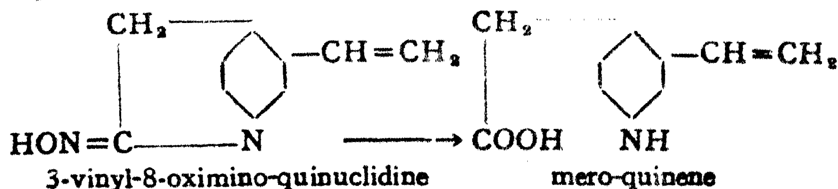
quinine

The possibility of the existence of a structure with a carbon bridge between the Natom and a carbon atom of the piperidine nucleus (quinuclidine structure) was established by the synthesis of β–ethyl–quinuclidine.



β-ethyl-quinuclidine

The point of linkage of the quinuclidine unit to the other half we settled by Rabe's investigations of the ketone obtained on gentle oxidation of cinchonine. [The latter differs from quinine only in the possession of a methoxy group in position 6 in the quinoline nucleus.] Cinchonine, on mild oxidation, gives the ketone cinchoninone. On treatment with nitrous acid (amyl nitrite in the presence of a minera acid), the latter decomposes into :–(*i*) cinchoninic acid, and (*ii*) oxime of 3–vinyl-8-oximino quinuclidine and the latter, on hydrolysis, gives hydroxylamine and mero-quinene. The oxime of 3-vinyl-8-oximino quinuclidine has the following structure which readily accounts for the products of hydrolysis :—



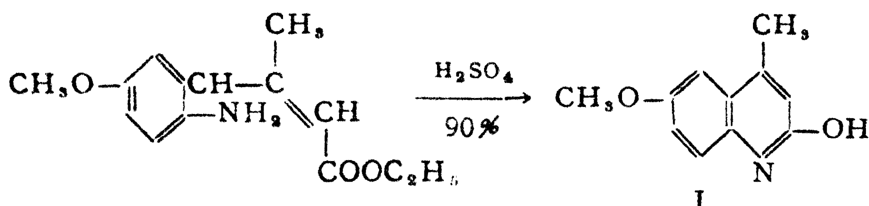
3-vinyl-8-oximino-quinuclidine mero-quinene

These results, therefore, indicate that quinuclidine unit must be linked to the quinolinic residue through the *CHOH* group by the carbon atom which appears as carboxyl group in meroquinene.

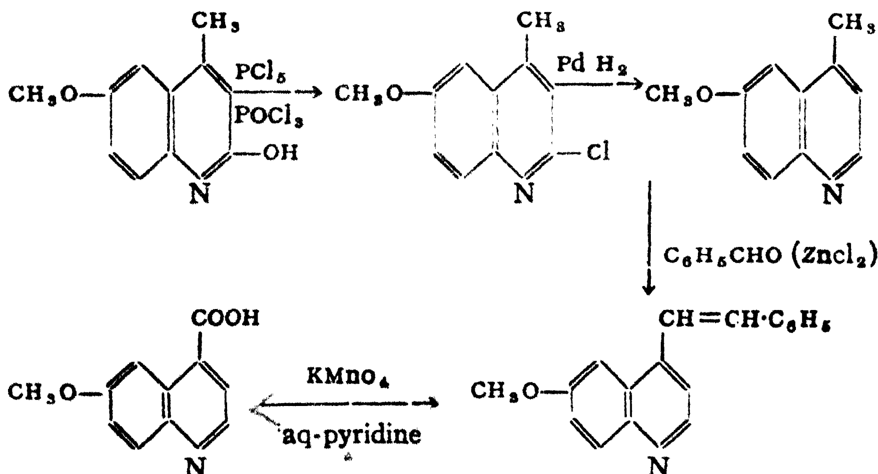
Synthesis of quinine.—Rabe and collaborators have synthesised dihydro-quinine and hydro-quinidine, which occur in the cinchona bark and can be obtained from quinine by hydrogenation. They are probably stereo-isomeric forms. The total synthesis consisted of :—

(*i*) Synthesis of quininic acid, (*ii*) synthesis of homo-cincholoipon and (*iii*) synthesis of hydroquinine. It is based on the relationship existing between qninine and quino-toxine. The latter is formed from the former, by the hydramine fission when heated with acetic acid. It is isomeric with quinine but is more toxic and hence called quino–toxine. Recently, Woodward and Doering have achieved a complete synthesis of quinotoxine and hence a successful synthesis of quinine itself. The synthesis involves synthesis (*i*) of quininic ester, (*ii*) of homo–mero–quinene ester and of (*iii*) quinotoxine and (*iv*) quinine.

Quininic ester.—Aceto acetic ester is condensed with *p*-anisidine to form 6-methoxy 4-methyl-2-hydroxy-quinoline (I).

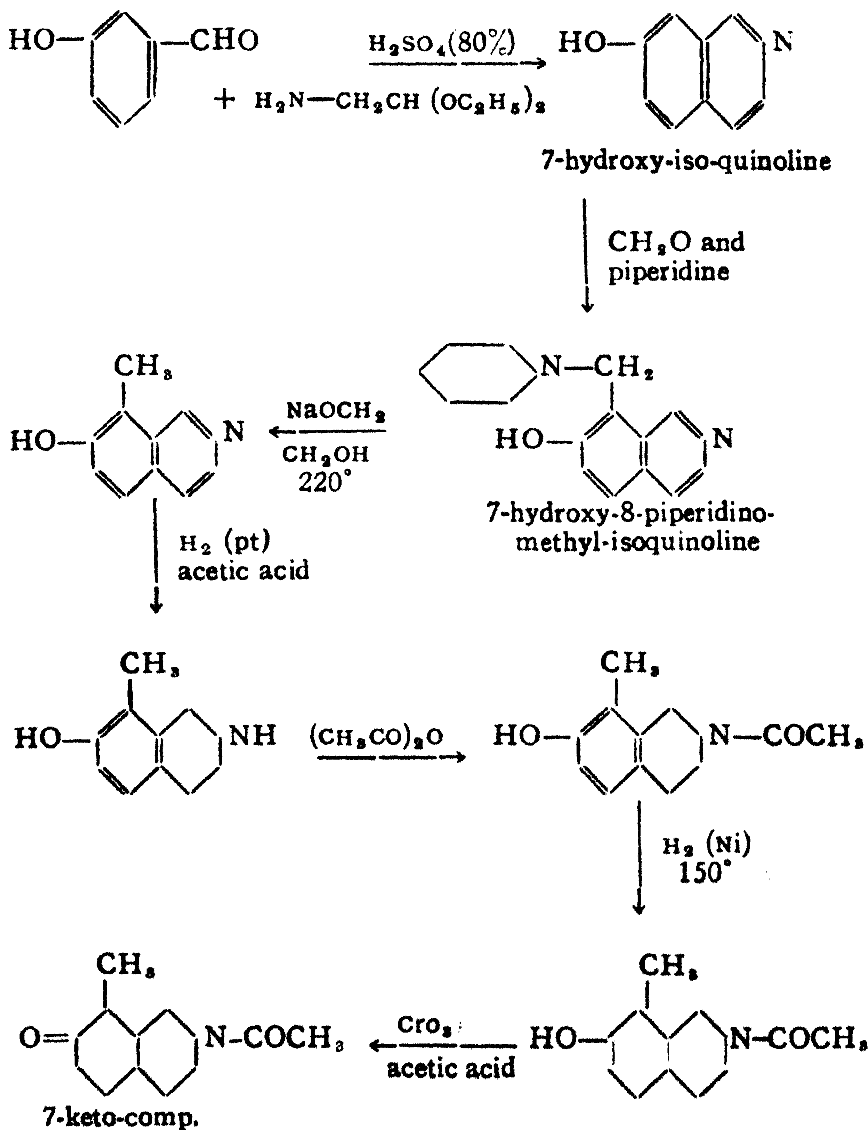


The latter is, then, converted into quininic acid by elimination of the hydroxyl group and subsequent oxidation of the methyl group in an indirect way :

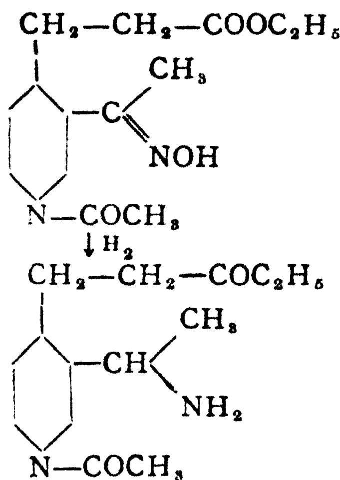


The acid is then esterified in the usual way to give the ethyl ester.

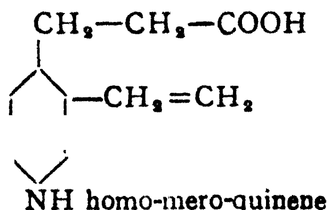
Homo-mero-quinene :—The steps involved are formulated as under :—



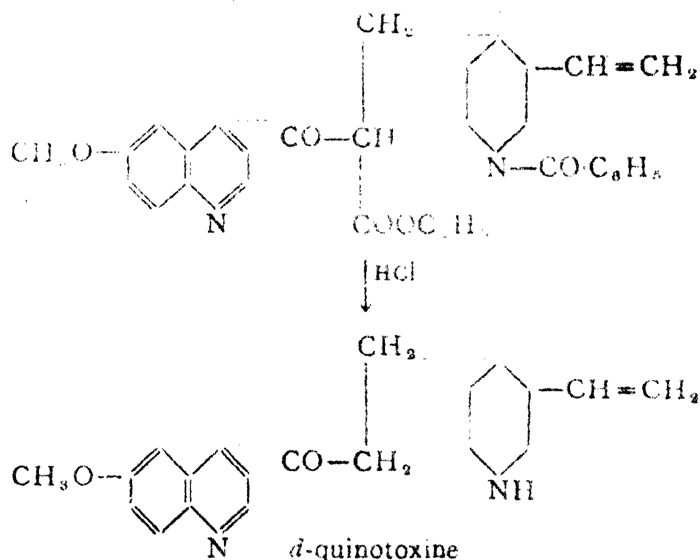
The 7-keto compound on treatment with ethyl nitrite and $NaOC_2H_5$ is converted into N-acetyl-10-oximino-dihydro-homemeroquinene ethyl ester, which is catalytically reduced to the corresponding amino compound.



The amino compound on treatment with excess of CH_3I in C_2H_5OH and anhydrous K_2CO_3 is converted into the corresponding quaternary ammonium compound, The latter on treatment with 60% *NaOH* gives homo-quinene.

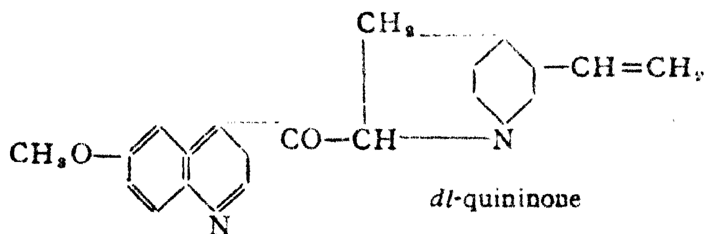


Synthesis of quinotoxine.—Homo'mero'quinene is benzoylated and the ethyl ester of N-benzoyl-homo'mero-quinene is condensed with excess of ethyl-quininate in presence of $NaOC_2H_5$ to give the β-keto ester which on hydrolysis and decarboxylation gives *dl*-quinotoxine.



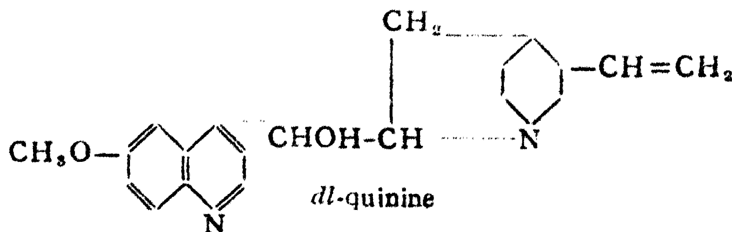
d-quinotoxine

This was resolved into *d* and *l*-quinotoxine by means of di benzoyl-*d*-tartaric acid. The *d*-quinotoxine is then converted into *l*-quinine by Rabe's method : the *d*-quinotoxine is treated with hypobromous acid ($NaOH+Br_2$) to give the N-bromoderivative which on treatment with $NaOC_2H_5$ is converted into quininone.



dl-quininone

which on reduction with H_2 in presence of Pd or Al in presence of $NaOC_2H_5$ gives *dl*-quinine.



dl-quinine

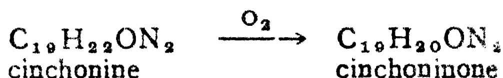
This is resolved by *d*-tartaric acid to give *l*-quinine, identical with the natural product.

CINCHONINE.—Cinchonine is the other cinchona alkaloid of some importance; it is the parent alkaloid of the cinchona series. Its constitution is based on the following analytical evidence.

(*a*) The molecular formula for cinchonine is $C_{19}H_{22}ON_2$ •

(*b*) On acetylation with acetic anhydride, a mono-acetyl derivative is formed. Thus the presence of a hydroxyl group is indicated.

(*c*) Mild oxidation of cinchonine yields a ketone, cinchoninone The hydroxyl group must, therefore, be a *secondary* alcoholic one (*CHOH*).

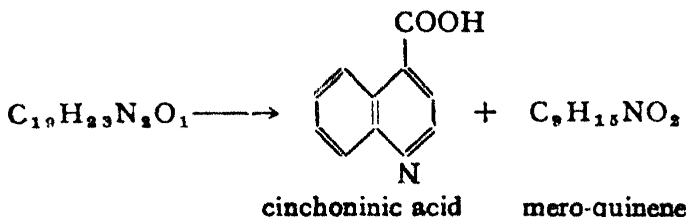


Nature of nitrogen.—This is revealed by the results of the various degradation methods.

(*a*) Treatment with hot concentrated sodium hydroxide yields among other products, (*i*) quinoline (*ii*) lepidine (4-methyl-quinoline) and (*iii*) a pyridine derivative.

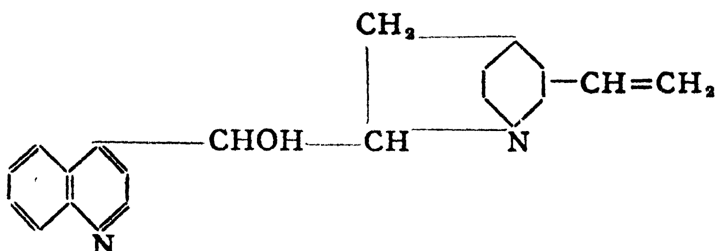
(*b*) On distillation with zinc dust, a large quantity of quinoline is obtained.

(*c*) Vigorous oxidation of cinchonine with chromic acid gives cinchoninic acid and mero-quinene:



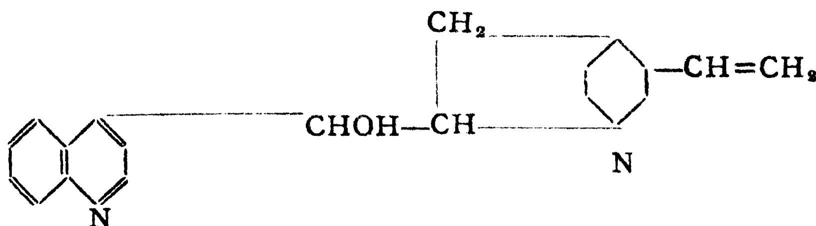
It is observed that the only difference between cinchonine and quinine is that the former does not carry a—OCH_3 group in the quinoline nucleus as quinine does. Quinine on oxidation with chromic acid gives quininic acid and mero-quinene. Hence the second half in cinchonine is identical with the second half in quinine.

Hence cinchonine may be assigned the structure:

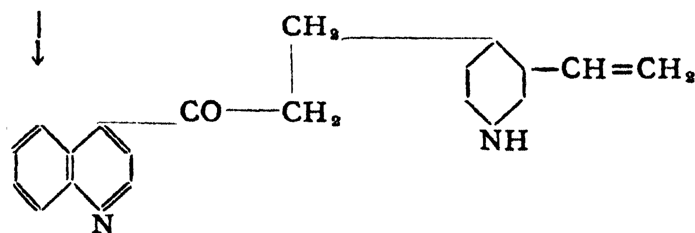


l-cinchonine

Rabe has reported a characteristic isomeric change undergone by cinchonine and other cinchona alkaloids. Cinchonine in the form of its salts, on heating with acetic acid for a long time, isomerised to cincho-toxine; the change is known as the '*hydramine fission*' and consists of the following structural alteration :—



l-cinchotoxine



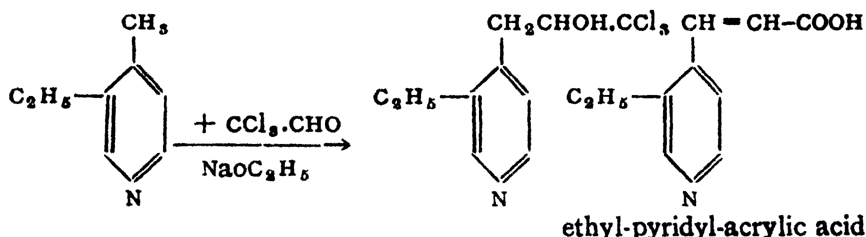
l-cinchotoxine

The products of the rearrangement are highly poisonous compounds and hence, the name "toxins." The toxins can be converted into the original alkaloids by the action of alkali hypobromite and subsequent condensation in the presence of sodium ethoxide (see synthesis of quinine). Another name for cinchotoxine is cinchonicine.

Robe and collaborators have synthesised hydroquinine and hydroquinidine, which occur in the cinchona bark; they can be also obtained from quinine by hydrogenation; they are probably stereoisomeric forms. The complete synthesis consists of (*a*) synthesis of quininic acid, (*b*) of homo-cincho-loipon and (*c*) of hydroquinine.

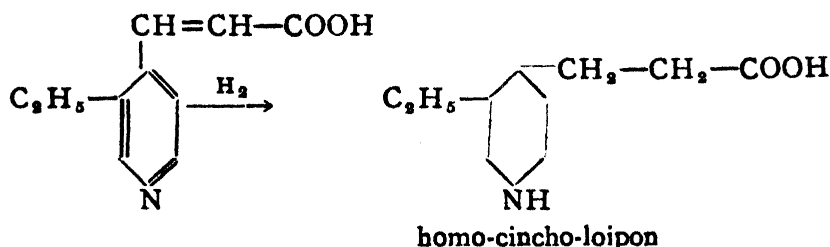
(*a*) The synthesis of quininic acid has been detailed earlier.

(*b*) *Synthesis of cincho-loipon,*—The starting point is *β* collidine. It is condensed with chloral in presence of sodium ethoxide to give ethyl-pyridyl acrylic acid :



ethyl-pyridyl-acrylic acid

A mixture of four stereo-isomers is formed which is resolved by *d*-tartaric acid. The optically active ethyl-pyridyl acrylic acid so obtained, is then reduced to ethyl-piperidyl propionic acid *i. e.* homo-cincho-loipon :—



homo-cincho-loipon

(*c*) *Synthesis of hydroquinine.*—The N-benzoyl derivative of homo-cincho-loipon ethyl ester is condensed with quininic ethyl ester in presence of sodium ethoxide: the compound thus formed is hydrolysed and decarboxylated to give N-benzoyl-hydro quinotoxine. The latter on acid hydrolysis gives hydro-quino-toxin.

$COOC_2H_5$ $\quad$ CH_3O- (quinoline ring, N) $\quad$ + $\quad$ $COOC_2H_5$ — CH_2 — CH_2 — (piperidine ring: $N-CO\cdot C_6H_5$, $-C_2H_5$)

N—benzoly-homo-cincho-loipon ethyl ester

$\downarrow NaOC_2H_5$

CH_3O- (quinoline ring, N) —CO—CH($COOC_2H_5$)—CH_2— (piperidine ring: $N-COC_6H_5$, $-C_2H_5$)

$\downarrow$

CH_3O- (quinoline ring, N) —CO—CH_2—CH_2— (piperidine ring: $N-COC_6H_5$, $-C_2H_5$)

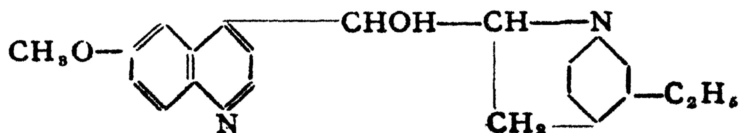
$\downarrow HCl$

CH_3O- (quinoline ring, N) —CO—CH_2—CH_2— (piperidine ring: NH, $-C_2H_5$)

hydro-quino-toxine

Hydro-quino-toxine was then changed into hydro-quinine by Rabe in the following way :— By the action of sodium hypo-bromite, *N*-bromo hydro-quino-toxine is first formed which is then converted into hydro-quininone under the influence of sodium ethoxide (elimination of one molecule of hydrobromic-acid see synthesis of quinine).

On reduction, di-hydro-quininone gives a mixture of hydro-quinine and hydro-quinidine which are stereo-isomers :



These synthetic products are identical with the natural bases found in the cinchona bark. Hydro-quinine contains the saturated ethyl group, in place the unsaturated vinyl group in quinine.

Cinchonidine, $C_{19}H_{22}N_2O_2$ and quinidine, $C_{20}H_{24}N_2O_2$ are isomeric with cinchonine and quinine respectively. They represent the respective stereo-isomerides. They are usually found together in the bark of the cinchona.

CUPREINE.—It is the alkaloid found in small quantity in the Remijia bark. On methylation, it is converted into quinine. It is thus, 6-hydroxy-cinchonine.

Alkaloids with Iso-quinoline Nucleus

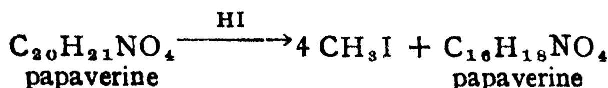
The most important alkaloids which belong to this class are those which comprise the *papaverine* proup. They occur closely associated together in opium and are derived from iso-quinoline. They are papaverine, laudanosine, laudanine, laudanidine, narcotine and narcine. Hydrastine found in species of Hydrastis also belongs to this group. Opium is the dried juice obtained from the unripe seeds capsules of the poppy. It is a rich source of alkaloids which can be subdivided into two groups: (*i*) the papaverine group: papaverine, laudanine and narcotine, derived from isoquinoline nucleus; and (*ii*) the morphine group; morphine, codeine, etc. These alkaloids are present in the seeds as the salts of organic acids like acetic and meconic.

PAPAVERINE.—It is a crystalline compound (m. p, 147°). It is a tertiary amine. It resembles morphine in its physiological properties, but is weaker in its action. It is isolated from the opium as follows:—The opium infusion is boiled with milk of lime, when the alkaloids of the morphine group go into solution, while those of the papaverine group are precipitated out. They are then extracted with a suitable solvent like chloroform, ether. Papaverine is then obtained by fractional solution or fractional precipitation from the mixture.

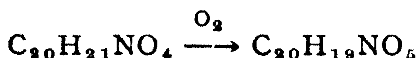
CONSTITUTION OF PAPAVERINE.—It possesses the molecular composition $C_{20}H_{21}NO_4$. Its structural formula rests on the investigation of Goldschmidt.

Nature of nitrogen atom.—This is revealed to be *tertiary* by the formation of the crystalline methiodide, $C_{20}H_{21}NO_4.CH_3I$.

Nature of oxygen atom.—Papaverine does not form any acetyl derivative with acetic anhydride, with indicates the absence of hydroxyl groups in the molecule. Zeisel's determination shows the presence of four methoxy groups. Hence, all the four oxygen atoms in the molecule are present as methoxy ($-OCH_3$) groups.

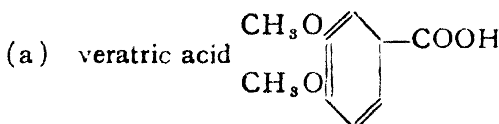


Nature of the structural units : Papaverine on oxidation with $KMnO_4$ in the cold gives papaveraldine which is a ketone.

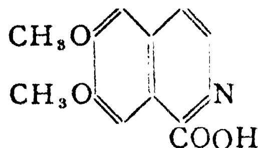


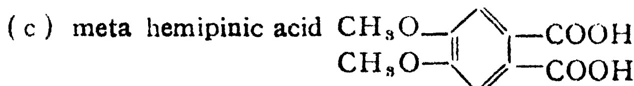
The formation of the ketone ($CH_2 \rightarrow CO$) indicates that there is a methylene groups ($-CH_2$) which is flanked by two nucleii: the nature of these two nuclei is established by results of vigorous oxidation and alkaline fusion of papaverine.

(1) Papaverine on oxidation with hot concentrated KMnO gives



(b) 6, 7 dimethoxy-iso quinoline - 1 - carboxylic acid



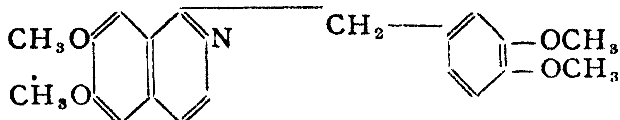


(d) pyridine, 2,3,4 tricarboxylic acid.

The products (c) and (d) are formed by the subsequent oxidation of (b). Alkaline fusion of both papaverine and papaveraldinc give 6,7, di-methoxy-is o quinoline, veratorle and small amounts of veratric acid.

These results therefore indicate that papavrine is built up of the veratrole and the 6, 7-dimethoxy-isoquinoline units. These units must be further linked up through the-CH_2—group (the presence which is indicated above). The veratrole unit is linked through the

position 4, (formation of varatric acid) and the isoquinoline nucleus is linked up through position 1. (formation of 6, 7, dimethoxy-isoquinoline -1- carboxylic acid), Hence papaverine must be



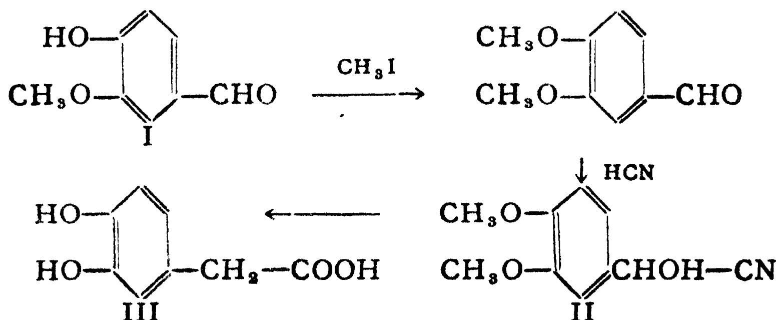
Finally, the above structure has been confirmed by a synthesis by Pictet and Gams. The important and essential steps in the synthesis are :—

(*i*) Synthesis of homo-veratroyl chloride, (*A*).

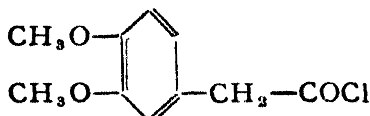
(*ii*) Synthesis of amino-aceto-ueratrone hydrochloride, (*B*).

(*iii*) Condensation of *(A)* and *(B)* to give papaverine.

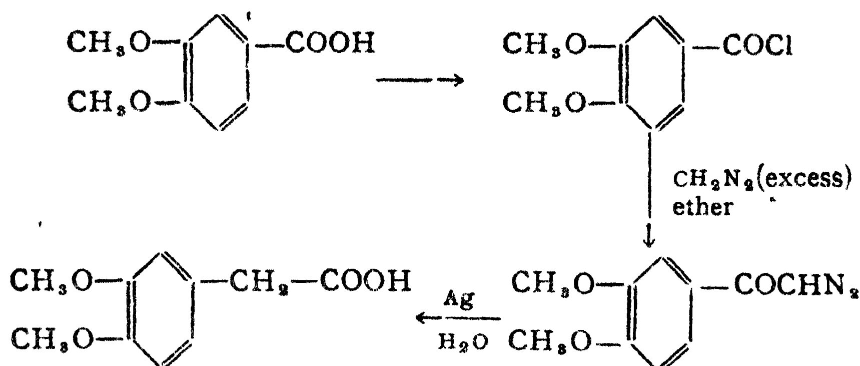
(*i*) *Synthesis of homo-veratroyl chloride, (A)*—The starting-point is vanillin (I). It is methylated with methyl iodide and treated with hydrocyanic acid to give the dimethoxy-mandelic nitrile (II) which is converted into homo-proto-catechuic acid, (III) by boiling with HI.



The above last conversion involves three different reactions: demethylation, ($OCH_3 \rightarrow OH$), reduction ($OH \rightarrow H$) and hydrolysis ($CN \rightarrow COOH$). The homo-proto-catechuic acid so obtained, on methylation and subsequent treatment with phosphorus pentachloride, is changed into homo-veratroyl chloride (*A*) :—

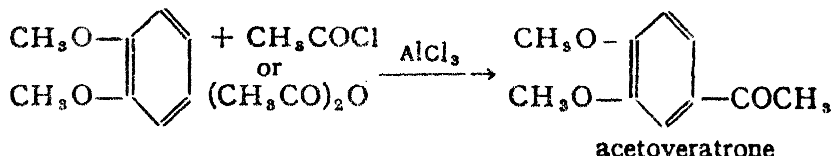


Recently, homoveratric acid has been synthesised by Arndt-Eistert's method of homologation. Tne steps involved are:—

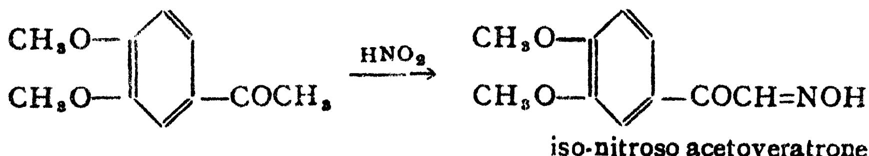


The acid is then converted into the chloride *A* with PCl_3.

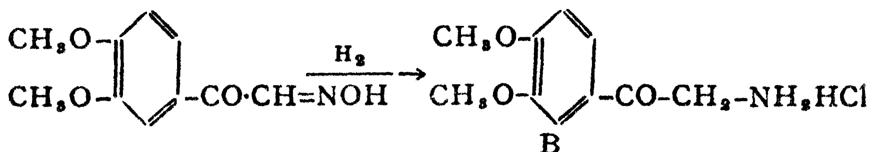
(ii) *Synthesis of amino-aceto-veratrone-hydrochloride,* (*B*):—Aceto-veratrone is obtained by the action of acetyl chloride or acetic anhydride on veratrole in presence of anhydrous aluminium chloride in nitrobenzene solution.



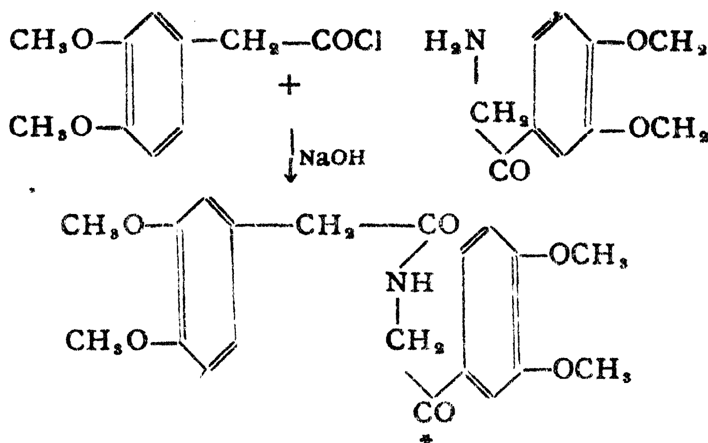
On treatment with nitrous acid (amyl nitrite and sodium ethoxide) acetoveratrone is converted into the corresponding iso-nitroso derivative :—



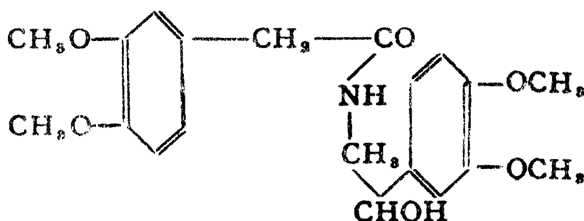
The latter, on reduction with stannous chloride and hydrochloric acid in excess gives the hydrochloride of ω-amio-aceto-veratrone (*B*) :—



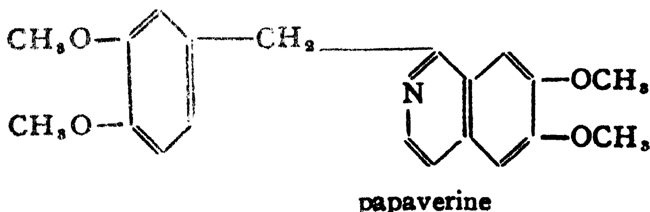
(*iii*) ***Condensation of*** (*A*) ***and*** (*B*) ***to papaverine*** :—Homo-veratroyl-chloride is condensed with the hydrochloride of ω-amino-aceto-veratrone in presence of alkali, to form homo-veratroyl ω-amino-aceto-veratrone :—



On reduction with sodium amalgam and alcohol (neutral). the true ketonic CO group. (marked with asterisk) is changed into *CHOH* group, giving homo-veratroyl-hydroxy—homo-veratryl-amine :—



Boiling with phosphorus-pentoxide in xylene solution, two molecules of water are lost and papaverine is formed.

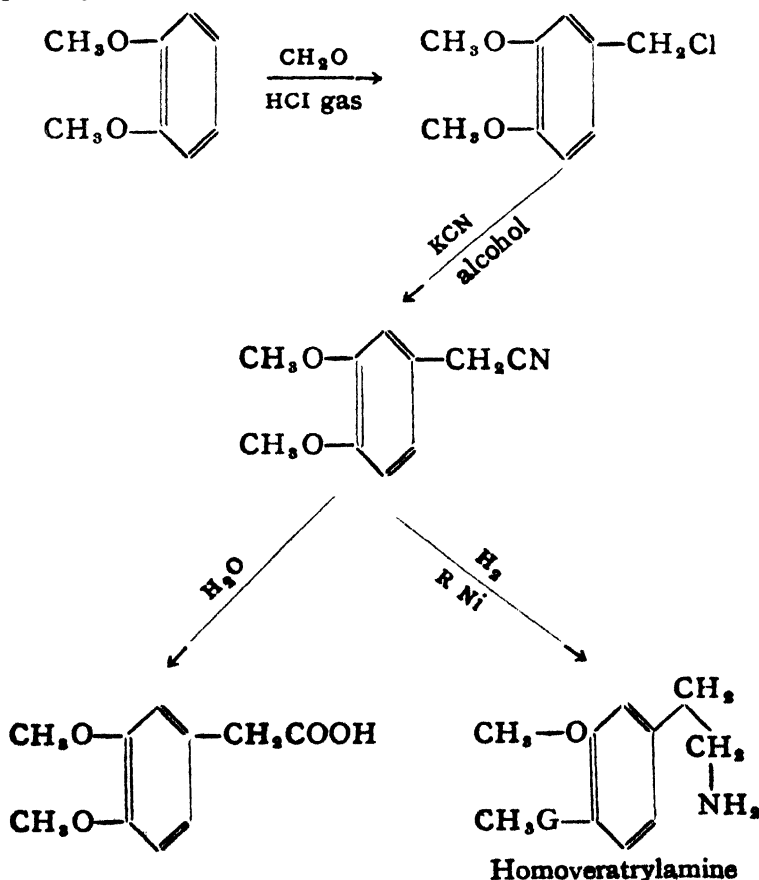


papaverine

The last reaction in which cyclodehydration of an acyl amino derivative is effected by the action of P_2O_5 in xylene to obtain the isoquinoline nucleus, is known as Bishler and Napierlaski's reaction. It is a general reaction; acyl derivatives of β-phenyl-

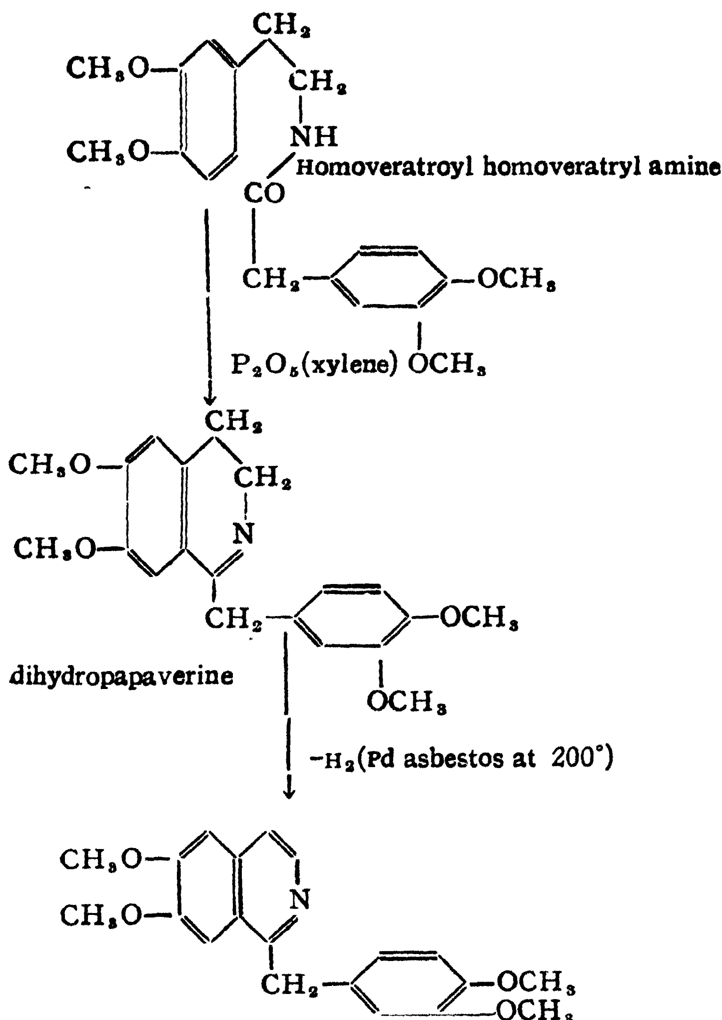
ethylamine are treated with a dehydrating agent like P_2O_5, $POCl_3$, $SnCl_4$ in benzene, toluene or xylene solution; $AlCl_3$ is sometimes used. Cyclo-dehydration takes place and a dihydro-iso-quinoline derivativie is obtained. The latter is then dehydrygenated with Pd on carbon at 200-220° or by heating with *S* or Se at high temperatures, to yield the corresponding iso-quinoline derivatives.

Bide and Wilkinson have considerably simplified and improved the above systhesis of papaverine. The two main reactants homo-veratric acid and homo-veratryl amine are both obtained from veratrole. The various steps involved in the complete synthesis are:



Homoveratrylamine

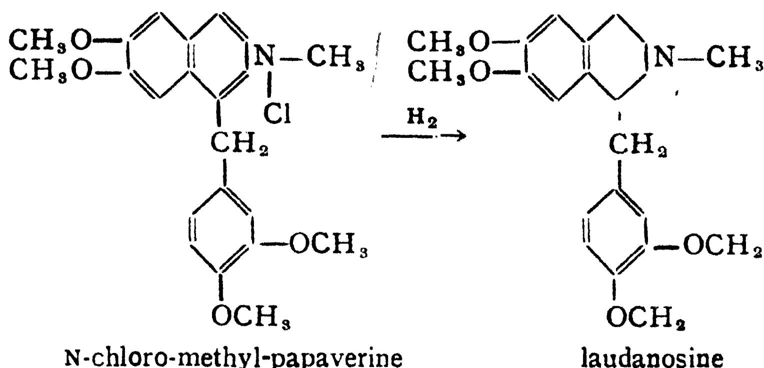
The homoveratric acid is convertad into the chloride by the action of PCl_5; the homoveratroyl chloride is then condensed with the homoveratroyl amine to give the homoveratroyl homoveratryl amine.



Papaverine is optically inactive. It resembles morphine in its physiological action, but is much weaker.

LAUDANOSINE—Laudanosine with the composition $C_{21}H_{27}NO_4$ is present in the opium alkaloids in very small quantities. Structurally it is closely related to papaverine, being its N-methyl-tetra-hydro derivative. The chloro-methyl derivative of

papaverine on reduction with tin and hydrochloric acid, yields the racemic form of laudanosine;

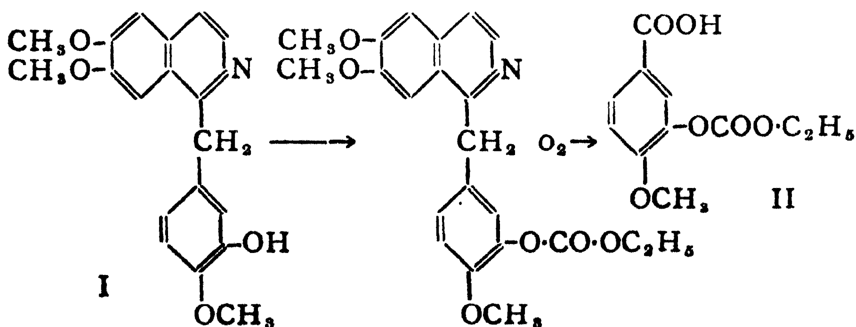


N-chloro-methyl-papaverine laudanosine

LAUDANINE:—It occurs in small quantities in opium. It has the molecular composition $C_{20}H_{25}NO_4$ which is less than that of laudanosine by CH_2; probably it contains one methoxy group less than laudnosine.

This is confirmed by its reaction with diazomethane in other, when it is converted into laudanosine (racemic). Thus it carries a free phenolic hydroxyl group. Spath has established the position of the free hydroxyl group in the following way:

Laudanine is changed into its carbo-ethoxy derivative by the action of chloro-formic ethyl ester. On oxidation, the latter forms carbo-ethoxy iso-vanillic acid (II) thus indicating that the free hydroxyl group is on the benzene nucleus of veratroyl residue. Hence, laudanine is (I) which would account for the above facts.



A total synthesis of laudanine has been accomplished.

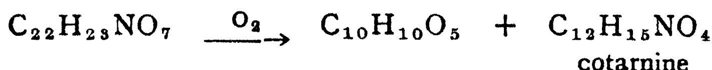
NARCOTINE :—Narcotine is one of the chief alkaloids of opium. Its molecular composition is $C_{22}H_{23}O_7N$. It contains no carboxyl or hydroxyl group in its molecule. The structural formula rests on the nature of the fission products obtained under different experimental conditions. Thus, we have :—

(*i*) On hydrolysis with $Ba(OH)_2$ or sulphuric acid at 140°- narcotine is converted into opianic acid and hydro-cotarnine.



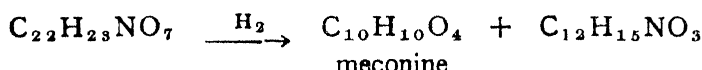
$$\underset{}{C_{22}H_{23}O_7N} \longrightarrow \underset{\text{opianic acid}}{C_{10}H_{10}O_5} + \underset{\text{hydro-cotarnine}}{C_{12}H_{15}NO_3}$$

(*ii*) Narcotine, on oxidation with nitric acid or with ferric chloride gives opianic acid and cotarnine.



$$C_{22}H_{23}NO_7 \xrightarrow{O_2} C_{10}H_{10}O_5 + \underset{\text{cotarnine}}{C_{12}H_{15}NO_4}$$

(*iii*) Reducing agents like zinc and hydrochloric acid or Na-amalgam convert narcotine into meconine and hydro-cotarnine.



$$C_{22}H_{23}NO_7 \xrightarrow{H_2} \underset{\text{meconine}}{C_{10}H_{10}O_4} + C_{12}H_{15}NO_3$$

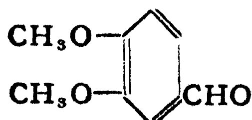
Meconine is simply related to opianic acid, as the latter, on reduction, is quantitavely changed into meconine. Similarly, hydro-cotarnine and cotarnine are closely related. These results of degradation by different reagents, therefore, definitely show that narcotine is built up of the opianic acid nucleus and the hydro-cotarnine nucleus.

Structure of opianic acid :—Opianic acid has the molecular composition $C_{10}H_{10}O_5$.

(*a*) It forms a mono-sodium salt and hence, is a monobasic acid.

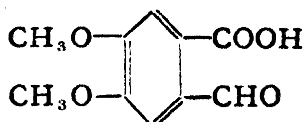
(*b*) On heating with hydriodic acid, two moles of methyl iodide are formed, thus indicating the presence of two methoxy groups.

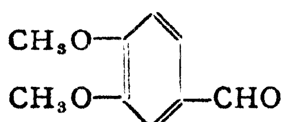
(*c*) On heating with soda-lime, it suffers decarboxylation and forms veratric aldehyde which has the structure :—



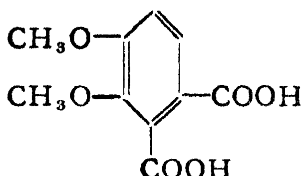
veratric aldehyde or methyl ether or vanillin.

Hence opianic acid is the carboxylic derivative of veratric aldehyde, and may be formulated either as I or II.



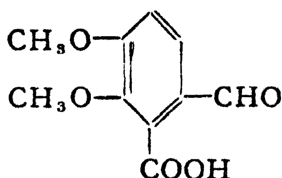


The final choice between the two formulæ rests on the fact that on oxidation, opianic acid gives hemipinic acid. The latter is an unsymmetrical molecule, as on esterification, it gives a mixture of two isomeric mono-esters. Hence, it has been assigned the formula.

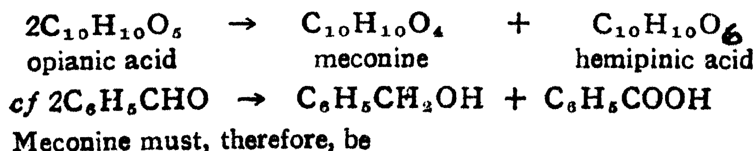


hemipinic acid

Such an acid would result from II on oxidation; hence opianic acid must be represented by II.



The *constitution of meconine* follows from that of opianic acid. When heated with concentrated potassium hydroxide opianic acid gives meconine and hemipinic acid by dismutation :

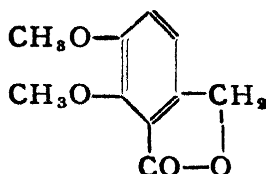


$$2C_{10}H_{10}O_5 \rightarrow C_{10}H_{10}O_4 + C_{10}H_{10}O_6$$

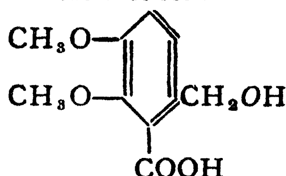
opianic acid → meconine + hemipinic acid

cf $2C_6H_5CHO \rightarrow C_6H_5CH_2OH + C_6H_5COOH$

Meconine must, therefore, be

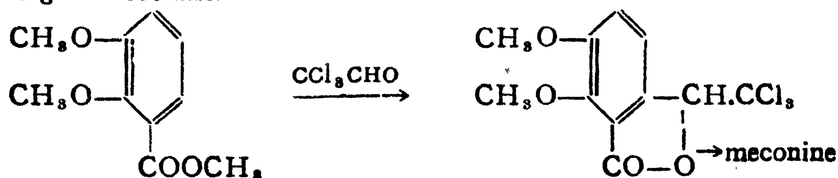


which is the lactone from the alcohol :



The lactone formula for meconine is justified as it does not give any reactions of a free carboxyl group.

Synthesis of meconine.—Guaiacol carboxylic acid is methylated to give the methyl ester of 2, 3 dimethoxy-benzoic acid (A). It is then condensed with chloral to give 5, 6 dimethoxy-trichloromethyl phthalide (B). The latter is hydrolysed and subsequently heated to give meconine.



Constitution of cotarnine.—The molecular composition of cotarnine is $C_{12}H_{15}N_4O_4$. It is a *secondary* base, as it forms with methyl iodide, cotarno-methine-methyl iodide $C_{12}H_{14}O_4N.(CH_3)I$. The latter, on heating with caustic soda, gives, trimethylamine and cotarnone with the composition $C_{11}H_{10}O_4$ which is an aldehyde. Oxidation of cotarnone with potassium permanganate, forms cotarno-lactone, $C_{11}H_{10}O_6$ and finally, an acid, cotarnic acid $C_{10}H_8O_7$.

Cotarnic acid is a dibasic acid which readily gives an anhydride. It contains one methoxy group and on heating with phosphorus and hydriodic acid at 160°, forms gallic acid.

These results indicate that cotarnic acid is a benzene derivative and should possess the following groups :—

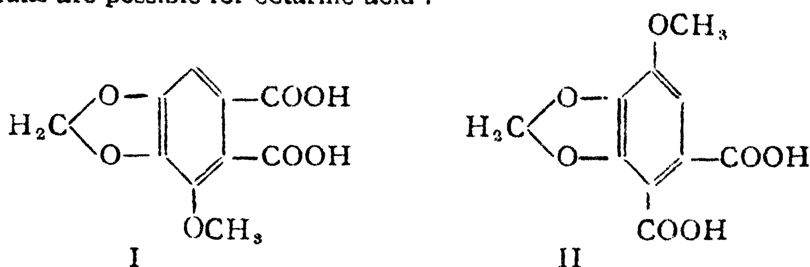
(*a*) two carboxyl groups in *ortho* position.

(*b*) one methoxy group, and

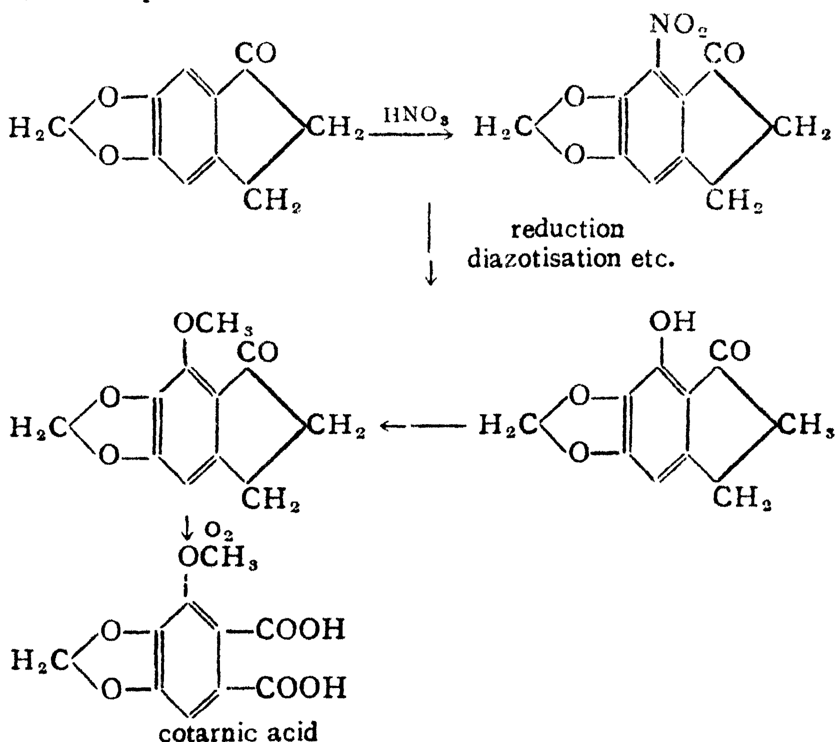
(c) two hydroxyl groups which are probably present as

methylene ether group, $H_2C\langle^{O-}_{O-}$;

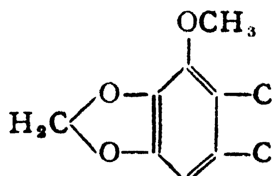
Also, the methoxy group and the methylene ether group must be in ortho-position, because demethylation gives gallic acid wherein all the three hydroxyl groups are vicinal, Hence, two formulæ are possible for cotarnic acid :—



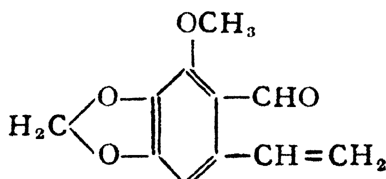
The final structure for cotarnic acid was established by a synthesis by Perkin, Robinson and co-workers. The starting point in the synthesis is 5-6-methylene-di-hydroxy-hydrindone. The various steps are :—



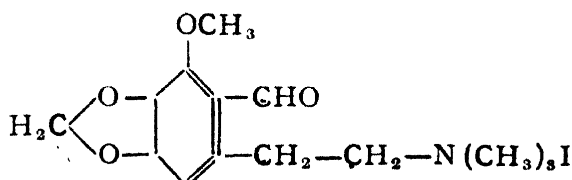
Now, cotarnic acid is obtained from cotarnone. The latter must, therefore, contain the same carbon skeleton as cotarnic acid *viz.* :—



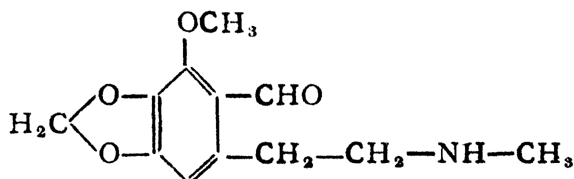
But cotarnone is an aldehyde; hence, we have :—



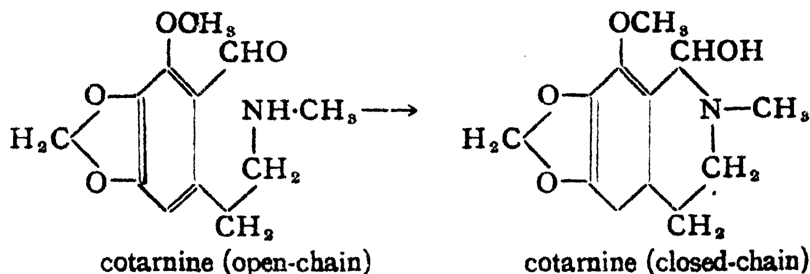
Further, it is obtained by the distillation with alkali of the quaternary ammonium salt, cotarno·methine-methylliodide. The latter must, therefore, be represented by :—



Hence, cotarnine is :



However, this formula fails to account for the formation of apophyllenic acid (which is a pyridine derivative), on oxidation with nitric acid. But the presence of a pyridine nucleus in the cotarnine molecule can be shown by assuming an intra-molecular ring formation to have occurred within the molecule :—

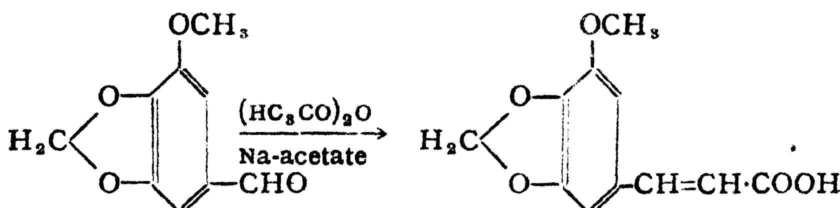


cotarnine (open-chain) cotarnine (closed-chain)

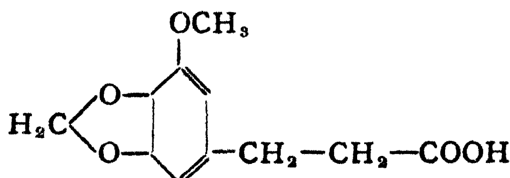
In fact, cotarnine reacts according to both the open-chain and cyclic formulas depending on the experimental conditions. With hydroxylamine, or with acetone, the corresponding open-chain condensation products are formed.

Synthesis of cotarnine.—The essential steps in the synthesis are :—

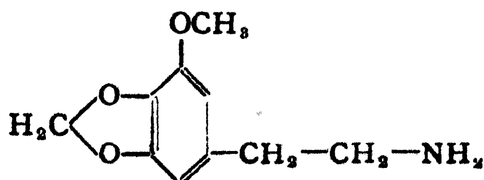
(*a*) Myristicin aldehyde is condensed with sodium acetate and acetic anhydride, to form the corresponding cinnamic acid derivative :—



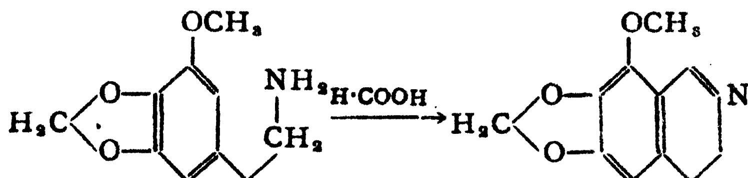
which is reduced with sodium amalgam to the corresponding propionic acid derivative :—



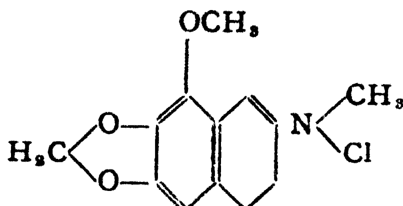
The above acid is converted into the corresponding amide and and then to amine by Hofmann's reaction.



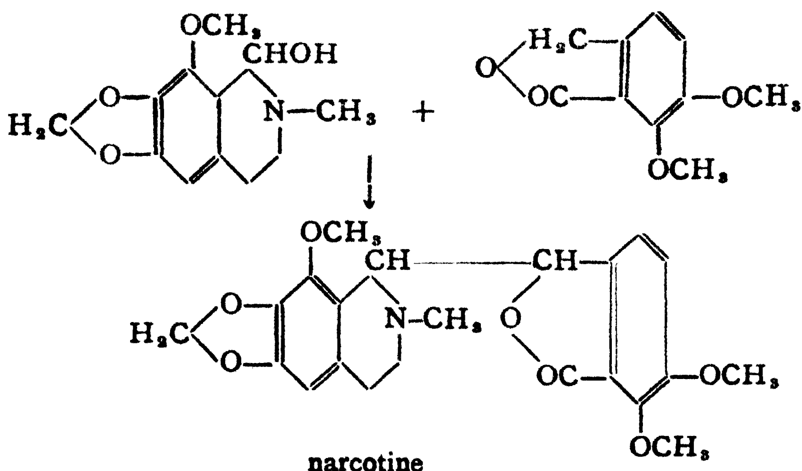
The amine is further condensed with formic acid and converted into an isoquinoline derivative :



The methochloride obtained by the action of methyl chloride is found to be identical with cotarnine chloride.



Structural formula for narcotine.—Narcotine is built up of the cotarnine and meconine units. The probable mode of linking of these units is through a carbon atom. Meconine and cotarnine react in alcoholic solution in the presence of potassium carbonate to form the racemic narcotine. It is resolved into optical isomers by bromo-camphor-sulphonic acid.



narcotine

Alkaloids with the Phenanthrene Nucleus

Opium the concentrated extract of the seeds of poppy contains, besides the alkaloids of the papaverine group, other alkaloids with a different nucleus. They include morphine, codeine and thebaine. They are very closely related to one another and all of them contain

the phenathrene nucleus. Morphine is the most important of all the alkalods of opium and finds extensive application in medicine to relieve pain.

STRUCTURE OF MORPHINE.—Morphine has the molecular compositions $C_{17}H_{19}NO_3$ and is a tertiary base containing N—methyl group. I is soluble in alkalies. thus, indicating the presence of a phenolic hydroxyl group. The nature of the nucleus present is revealed by the studies in degradation of the codeine molecule. The latter possesses the molecular composition $C_{18}H_{21}NO_3$ and is a mono-methyl ether of morphine, and accordingly morphine can be methylated to give codeine. Codeine gives the following reactions from which the structural skeletons of morphine and codeine molecules have been deduced.

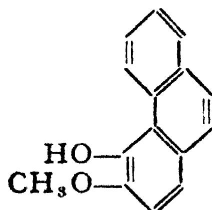
(*a*) On mild oxidation, codeine gives a ketone, codeinone $C_{18}H_{19}NO_3$. This indicates the presence of a *secondary* alcoholic group.

(*b*) Distillation of codeine or morphine with zinc dust gives phenanthrene. Hence, both the alkaloids must contain the phenanthrene nucleus.

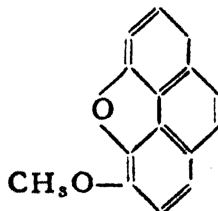
(*c*) When codeine-methyl-ammonium-iodide is boiled with sodium hydroxide, a tertiary base, α-methyl-morphi-methine, $C_{12}H_{23}O_3N$ is obtained. The latter, on heating with various reagents under different conditions, gives a variety of decomposition products. Some of the important and typical fission products are:—

(*i*) *Basic.*—$(CH_3)_2N—CH_2—CH_2OH$ (dimethyl amino-ethyl alcohol), dimethyl-amine and trimethyl-amine.

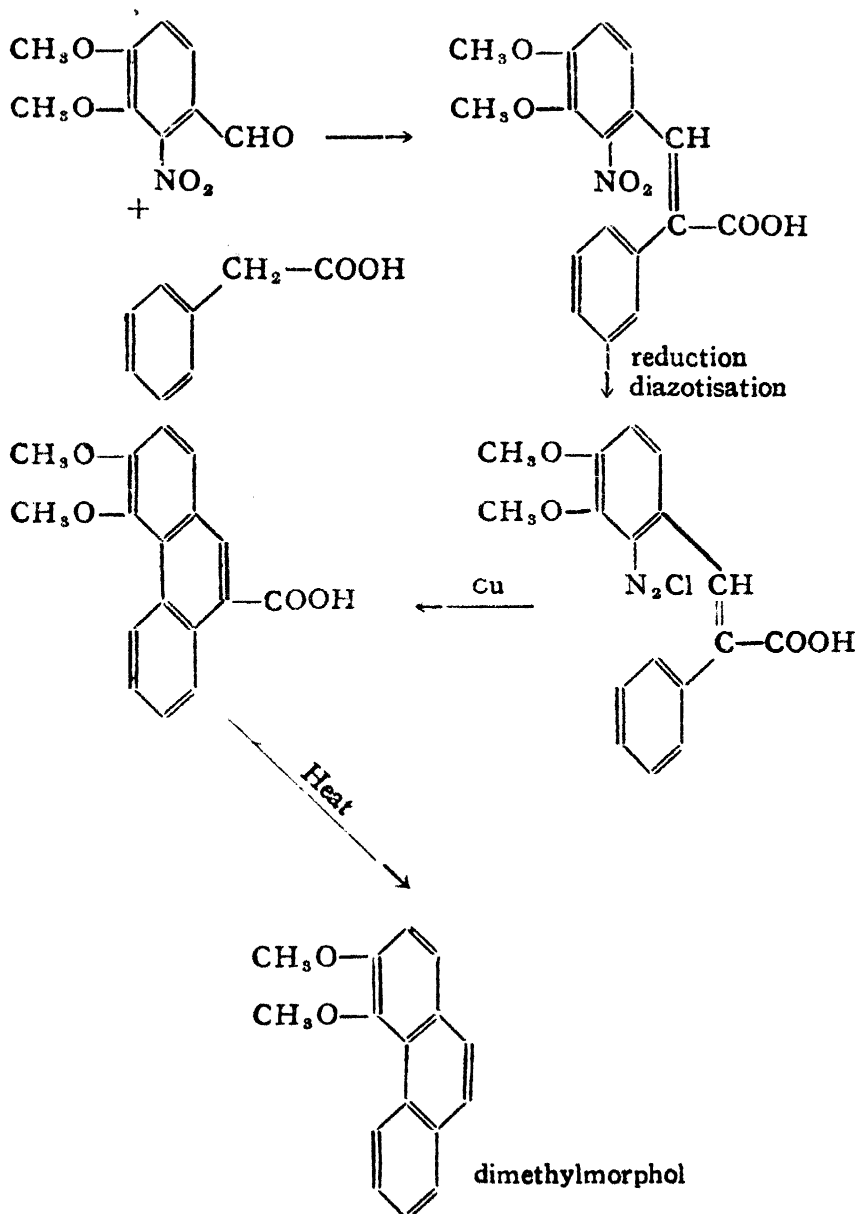
(*ii*) *Acidic.*—Methyl-morphol which has the structure :—



(*iii*) *Neutral*—Methyl-morphenol which has the stucture :—

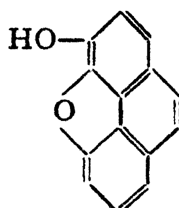


Now, morphol and its mono and di-methyl ethers have been obtained by syntheses which confirm their structures. Pschorr has reported the following method for the synthesis of morphol-dimethyl ether :—

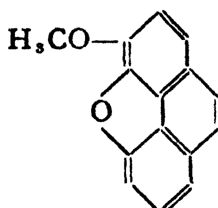


The mono-methyl ether can be synthesised in an analogous way starting from 2-nitro-4-hydroxy-4-methoxy-benzaldehyde and phenyl acetic acid.

Similarly, the constitutions of morphenol and its methyl ether have been established. They are :—



morphenol

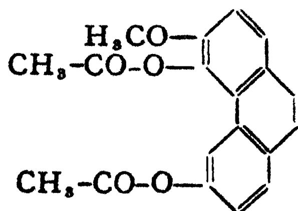


mono-methyl-morphenol

On reduction, morphenol is changed into morphol.

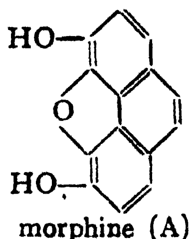
The foregoing considerations and results, thus definitely indicate that morphine and codine must contain the above structural units. The position of the secondary alcoholic group is revealed by the following evidence. Codeinone, the ketone obtained from codeine with chromic acid oxidation, on long boiling with acetic anhydride, is decomposed into :—

(*a*) $CH_3—NH—CH_2—CH_2OH$, monomethyl-amino ethyl alcohol and (*b*) 3-methoxy-4-6-di-acetyl phenanthrene :—

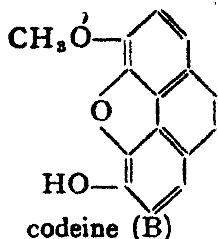


i.e. the secondary alcoholic group is in position 6.

From the above-mentioned evidence the carbon skeletal formulas for morphine and codeine may be formulated as A and B respectively.



morphine (A)



codeine (B)

Thus the three oxygen atoms in morphine possess different functions. One of them is phenolic and confers on the alkaloid acidic properties and solubility in alkali. It can be methylated with methyl iodide in presence of alkali, or with phenyl triethyl ammonium hydroxide (which does not give quaternary *N*-compounds) and the methylation gives codeine; codeine is thus the phenolic methyl ether or morphine.

The second oxygen atom in morphine and in codeine also, is present as a secondary alcoholic group as codeine can be oxidised to codeinone. The third oxygen atom is very inert and occurs as an ether linkage.

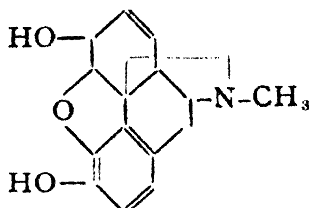
The skeleton A contains 14 carbon atoms which belong to the phenanthrene nucleus.

To this skeleton, the nitrogen atom which is tertiary and which carries a methyl group must be so linked as to form the earlier mentioned basic fission products like di-methyl, or mono-methyl-amino-ethyl alcohol with the ethanamine chain: CH_3—N—C—C.

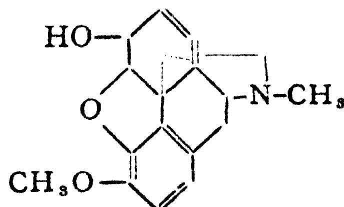
The ready formation of the above products indicates that the *N* atom is linked with two carbon atoms in a chain which is easily separated as a whole from the phenanthrene nucleus. The point of linking of the nitrogen atom to the nucleus is established by the studies in degradation of 9-hydroxy-codeine, which is obtained by gentle oxidation of codeine. The hydroxy-codeine is first changed into a ketone. This indicates that the hydroxyl group is on a carbon atom such that it becomes unsaturated with the opening up of the nitrogen ring.

Further, the acetolysis of the methine yields a methoxy-diacetoxy-phenanthrene derivative that can be oxidised to 9–10

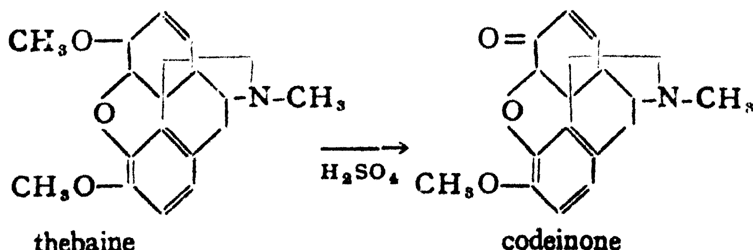
phenanthrene-quinone with the elimination of the two acetoxy groups. Hence, the hydroxyl group must be in position 9 or 10 and the ethanamine chain must be attached in one of these positions. However, the chain is so labial that any conclusion drawn regarding its exact location must be taken with reservation. Schopf has proved that the chain is located at position 13 and not 14. Robinson has proposed the following formula for morphine which has been widely accepted :—



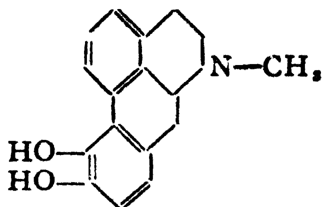
The corresponding phenolic methyl ether is codeine.



Thebaine is the methyl ether of the enolic form of the ketone codeinone. On hydrolysis with dilute acids, thebaine is converted into codeinone.

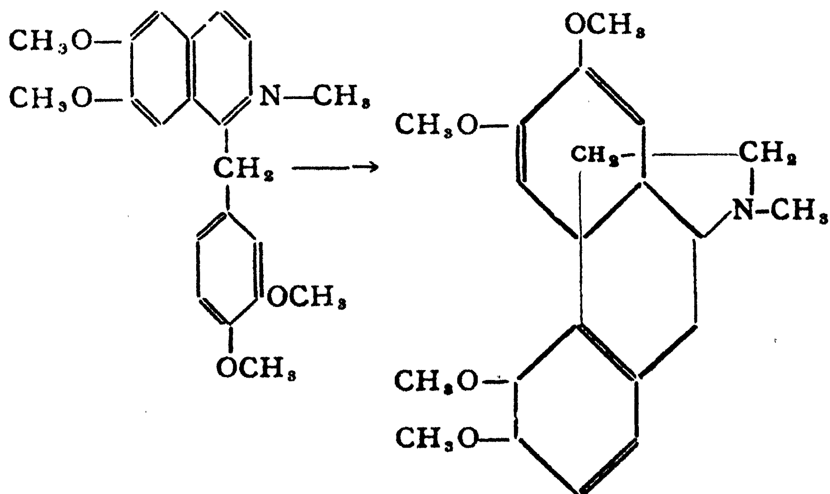


Apo-morphine is a product of dehydration of morphine. It is formed when morphine is heated with hydrochloric acid at 140-150°. Its structure has been formulated as below :—



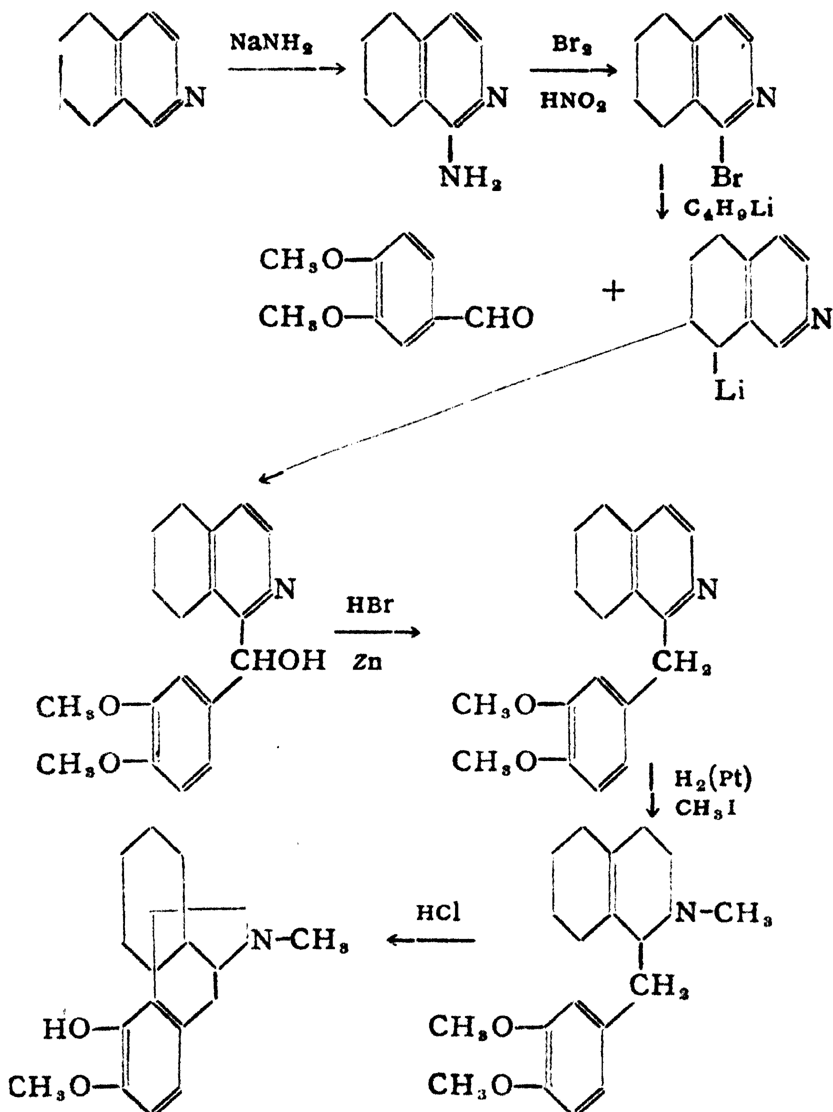
Hence, it contains a condensed phenanthrene-iso-quinoline nucleus. The dehydration which takes place at positions 5 and 6 is accompanied by (*a*) formation of a benzene ring, (*b*) shift of the nitrogen bridge and (*c*) the formation of an iso-quinoline system; the dehydration can also be effected with sulphuric acid and phosphoric acid. The above structure has been confirmed by two independent syntheses of the dimethyl ether of apo-morphine.

The synthesis of the ring system present in the morphine alkaloids has offered the greatest difficulty. Recently, a method based on biogenetic consideration by Robinson, has been developed by Grewe. According to Robinson, the papaverine alkaloids constitute the precursors of the mere complicated morphine alkaloids, with which they are associated in nature. A possible biogenetic route from laudanosine—a papaverine alkaloid—to morphine may be indicated as follows :



laudanosine morphine system

Grewe has actually realised the new type of ring closure and accomplished the synthesis of a degradation product (D) containing the C—N skeleton of the morphine molecule. The steps involved are indicated below :



This synthesis also clearly indicated that the ethanamine chain of morphine alkaloids is linked at C_{13} as earlier postulated in the Robinson's formula for morphine.

Synthetic Substitutes

Many natural alkaloids, because of their physiological properties, have found great applications in medical practice from time immemorial. Quinine is still the antimalarial of choice. The morphine alkaloids constitute the most efficacious remedy to relieve physical pain. Atropine is used in ophthalmic surgery to dilate the pupil of the eye. The ergot alkaloids are employed to induce the mobility of the uterus. Lastly cocaine, the chief alkaloid of Coca leaves is an excellent local anæsthetic. But all of these natural products are extremely poisonous and the therapeutic dose has to be assessed very accurately. The isolation of an individual alkaloid in the pure condition is not only arduous and difficult, but it is expensive; the use of crude preparations on the other hand, necessitates a careful standardisation; the latter is rendered difficult as the natural product is a complex mixture whose composition varies widely with many factors like climate, season, age of the plant and the soil.

The production of synthetic alkaloids also presents highly complicated chemical and engineering problems; and as many of them exhibit highly toxic side effects, their production does not offer any advantages. Hence, attention has been directed from the beginning, to the production of substitutes. Such a mode of approach has an additional advantage; the substitutes obtained may be made to possess only the beneficial effect of the original natural product. Thus, it was Einhorn who in 1892, initiated the search for a cocaine substitute which possessed only the useful properties of the natural product. A brief account of the several attempts made from time to time to synthesise the substitutes for the different natural alkaloids, will be given below.

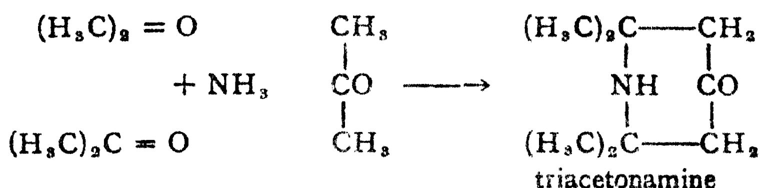
SUBSTITUTES FOR ATROPINE.—Atropine is an ester of tropine. Ladenburg prepared a number of other esters which he called collectively as *tropeines*. Some important tropeines synthesised are:—

benzoyl tropeine	... $C_8H_{14}NO\text{-}OC\text{-}C_6H_5$
cinnamyl tropeine	... $C_8H_{14}NO\text{-}OC\text{-}CH=CH\text{-}C_6H_5$
salicyl tropeine	... $C_8H_{14}NO\text{-}OC\text{-}C_6H_4\text{-}OH$
homatropine	... $C_8H_{14}NO\text{-}OC\text{-}CHOH\text{-}C_6H_5$

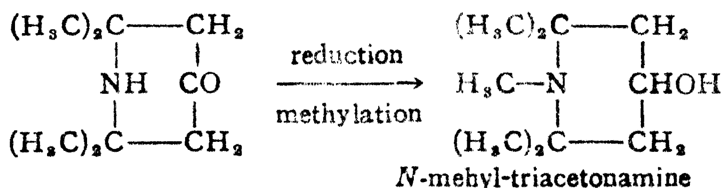
The first three tropeines unlike atropine, possess no mydriatic properties, homatropine, on the other hand, has the property of dilating the pupil of the eye. These observations have led to the

view that mydriatic action of a tropeine rests on the presence of an alcoholic group (*CHOH*—) in the aromatic-aliphatic acid residue. Homatropine is a much weaker poison than atropine and is used in eye surgery. Another modification consists in the use of a simpler alkamine obtained from triacetonamine, in place of tropeine, in the preparation of the substitute compounds.

Triacetonamine is formed by the condensation of ammonia and acetone :—



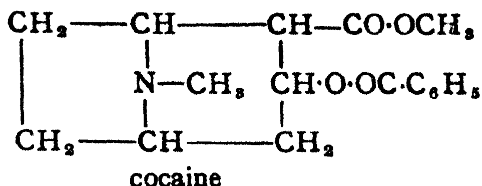
Reduction and methylation give the *N*-methyl-triacetonamine :—



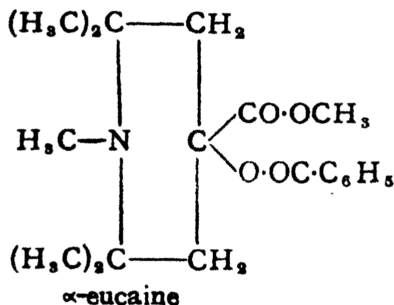
The mandelic ester of this alkamine shows mydriatic properties.

SYNTHETIC SUBSTITUTES FOR COCAINE.—Cocaine is highly toxic and is a habit-forming drug. Also, when used for injections, it possessess obvious disadvantages. Its solutions do not keep well but become mouldy and decompose on boiling and hence, they cannot be readily sterilised. It is for these reasons and on acconnt of the high price of cocaine, that systematic attempts have been made to replace cocaine by analogous synthetic preparations.

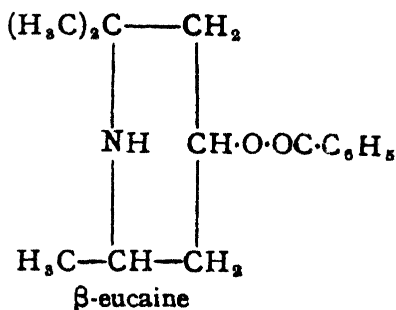
α-AND β-EUCAINES :—Cocaine is an ecgonine derivative and is structurally related to tropine. Atropine, a tropeine, possesses slight anæsthetic poperties. This observation led to the investigation of other tropeines or compounds with tropinelike structure. The most important of such substances are the two α-and β-eucaines. They are alkamine derivatives. They contain piperidine systems. They possess pronounced anæsthetic properties. The structural similarities between them and cocaine are obvious :—



cocaine

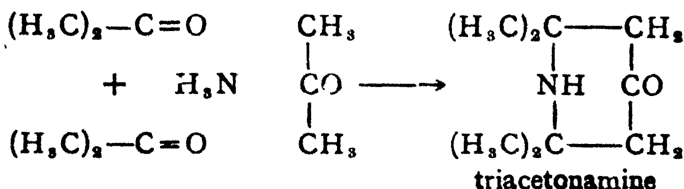


α-eucaine



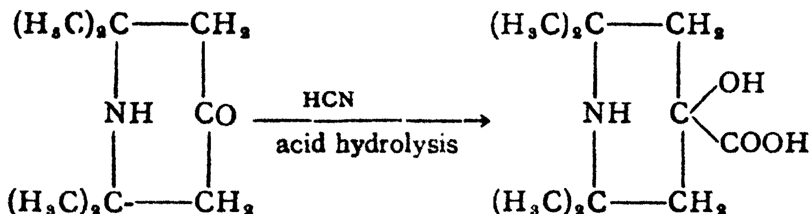
β-eucaine

α-Eucaine was obtained by Merling. Three molecules of acetone are condensed with one molecule of ammonia to yield triacetonamine:

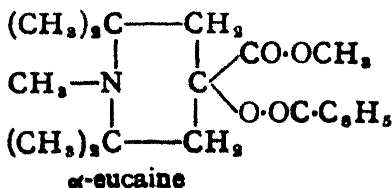


triacetonamine

The latter, on treatment with *HCN* and subsequent hydrolysis gives the corresponding carboxylic acid:—



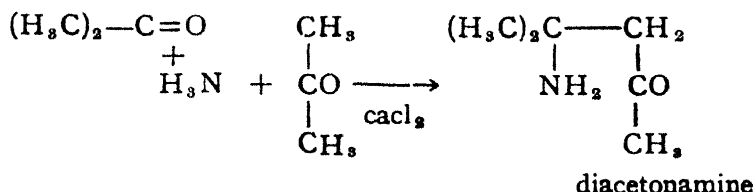
The acid, on benzoylation and methylation, gives α-eucaine.



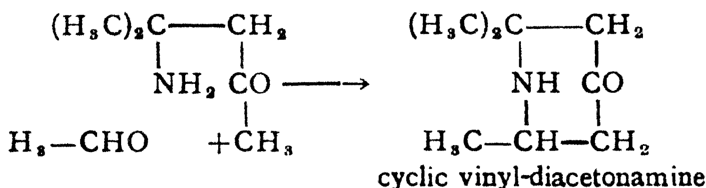
α-eucaine

It is a cheap substitute for cocaine. It is less toxic and stable to boiling water and hence, can be sterilised by boiling. But it is painful and irritant. It is now replaced by β-eucaine.

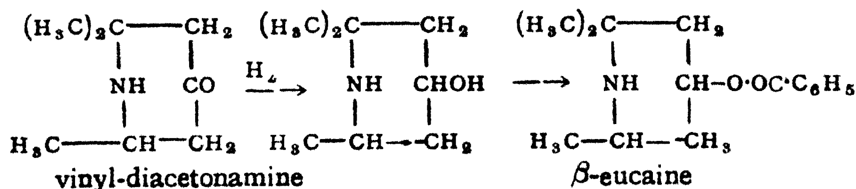
β-Eucaine is prepared from diacetonamine, which is formed by the condensation of two molecules of acetone and one of ammonia.



Diacetonamine in the form of its acid oxalate is condensed with acetaldehyde-acetal and C_2H_5OH to give the cyclic vinyl-diacetonamine.



On reduction with Na and alcohol and benzoylation, the vinyldiacetonamine is converted into β-eucaine :



The hydrochloride of the base is the drug, β-eucaine. It is stable to boiling and much less toxic than α-eucaine.

In addition to these closed-chain structure compounds related to tropine, simple open-chain alkamine esters have been synthesised and used as cocaine substitutes. A close study of cocaine has shown that the grouping $H_3C—N—CH—CH_2—CH—O{\cdot}OC{\cdot}C_6H_5$ in the molecule is responsible for the anæsthetic action. A number of compounds which contain the grouping $H_3C—N—C—C$

$C—OOC.C_6H_5$ or $N—C—C—O.OC.C_6H_5$ have been synthesised and found to be very successful anaesthetics. The most successful of such compounds are *stovaine and novocaine (procaine).*

STOVAINE.—Stovaine is prepared by the action of ethyl magnesium bromide on dimethyl amino-acetone and subsequent benzoylation of the product. The di-methyl amino-acetone is obtained from acetóne.

$$\begin{matrix} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{matrix} + Br_2 \xrightarrow[\text{ether}]{AlCl_3} \begin{matrix} CH_3 \\ | \\ CO \\ | \\ CH_2Br \end{matrix} \xrightarrow[\text{excess}]{NH(CH_3)_2} \begin{matrix} CH_3 \\ | \\ CO \\ | \\ CH_2\text{-}N(CH_3)_2 \end{matrix}$$

di-methyl-amino-acetone

$$\begin{matrix} CH_3 \\ | \\ CO \\ | \\ CH_2—N(CH_3)_2 \end{matrix} + C_2H_5MgBr \xrightarrow{H_2O} \begin{matrix} CH_3 \\ | \\ C \begin{matrix} \diagup OH \\ \diagdown C_2H_5 \end{matrix} \\ | \\ CH_2\text{-}N(CH_3)_2 \end{matrix} \xrightarrow{\text{benzoylation}} \begin{matrix} CH_3 \\ | \\ C \begin{matrix} \diagup O.OC.C_6H_5 \\ \diagdown C_2H_5 \end{matrix} \\ | \\ CH_2\text{-}N(CH_3)_2 \end{matrix}$$

di-methyl-amino-acetone | stovaine

Stavaine is used widely in producing spinal anaesthesia.

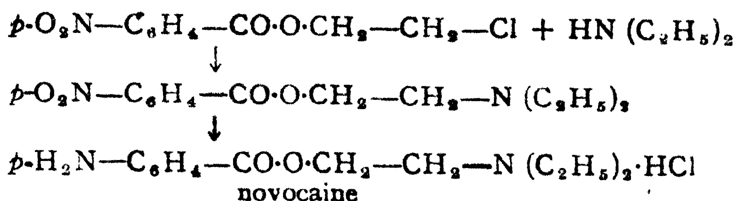
NOVOCAINE.—It is related to para-amino-benzoic acid. Einhorn and Heintz found that benzoyl derivatives of amino-hydroxy benzoic ester possessed distinct anæsthetic properties. Novocaine is the simple local anæsthetic of this type. It is the di-ethyl-amine derivative of ethyl-para-amino benzoate. It has the structure :—

$$H_2N—C_6H_4—COO{\cdot}CH_2—CH_2—N\,(C_2H_5)_2{\cdot}HCl$$

It is obtained as follows: *p*-nitrobenzoyl chloride is condensed with ethylene chlorohydrin in presence of pyridine to give the ester :

$$p\text{-}NO_2—C_6H_4—CO{\cdot}Cl + HO{\cdot}CH_2—CH_2Cl$$
$$\downarrow$$
$$p\text{-}NO_2—C_6H_4—CO{\cdot}O{\cdot}CH_2—CH_2—Cl$$

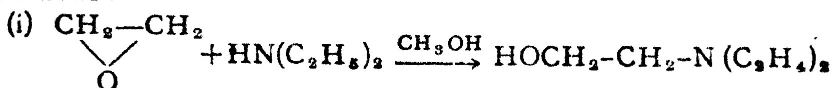
On amination with $NH\ (C_2H_5)_2$ and subsequent reduction of the nitro group by tin and hydrochloric acid, novocaine is formed:



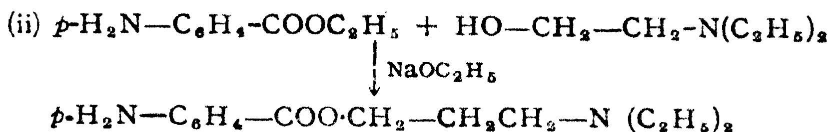
$$p\text{-}O_2N\text{—}C_6H_4\text{—}CO\cdot O\cdot CH_2\text{—}CH_2\text{—}Cl + HN(C_2H_5)_2$$
$$\downarrow$$
$$p\text{-}O_2N\text{—}C_6H_4\text{—}CO\cdot O\cdot CH_2\text{—}CH_2\text{—}N(C_2H_5)_2$$
$$\downarrow$$
$$p\text{-}H_2N\text{—}C_6H_4\text{—}CO\cdot O\cdot CH_2\text{—}CH_2\text{—}N(C_2H_5)_2\cdot HCl$$

novocaine

In a recent modification of the above method it is obtained as follows :—



(i) $CH_2\text{—}CH_2$ (epoxide, O) $+ HN(C_2H_5)_2 \xrightarrow{CH_3OH} HOCH_2\text{-}CH_2\text{-}N(C_2H_4)_2$



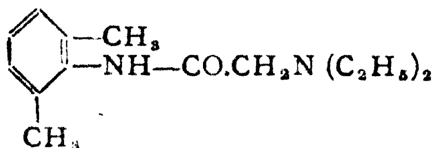
(ii) $p\text{-}H_2N\text{—}C_6H_4\text{-}COOC_2H_5 + HO\text{—}CH_2\text{—}CH_2\text{-}N(C_2H_5)_2$

$$\downarrow NaOC_2H_5$$

$$p\text{-}H_2N\text{—}C_6H_4\text{—}COO\cdot CH_2\text{—}CH_2CH_2\text{—}N(C_2H_5)_2$$

the hydrochloride of which, is the drug novocaine ; it is also known as procaine. It is non-irritant and a powerful anæsthetic but is only one-fourth as toxic as cocaine. It is also free from all after effects and is not habit-forming. It is the most widely used of the synthetic local anæsthetics.

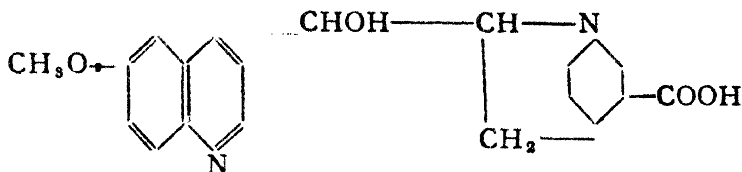
More recently, a new group of compounds belonging to the ω-amino acylanilide type have been developed as cocaine substitutes. The representative of this class is xylocaine, introduced by Lofgren. It has the structure :



It is more potent than procaine but also more toxic ; however, it possesses one advantage over the older drug in that it is unusually stable and its solution can be sterilised without decomposition.

Synthetic Quinine Substitutes or Antimalarials.—Quinine is still the most important anti-malarial used in modern medicine. Several attemps have been made to replace quinine by suitable synthetic substitutes. Earlier attempts were confined to the modification of the structure of the cinchona alkaloids. Such modified alkaloids were either the carboxyl acids obtained by oxidation of the vinyl group or their esters. Quitenine, the

carboxylic derivative from quinine with the following structure has been found to be inactive.

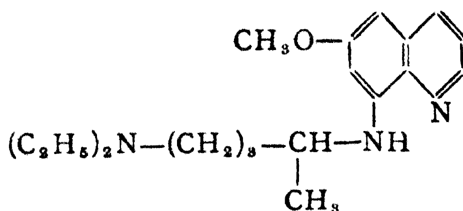


The alkyl esters are, however, found to possess anti-malarial activity, which increases as the homologous series is ascended and reaches a maximum with a butyl or amyl radical. But they are not as efficient as quinine.

Also quinine is not an ideal drug, as it attacks only certain forms of the malarial organism, and is unable to prevent relapses in some types of malaria. Hence a search for substitutes with increased activity and decreased toxicity was initiated in Germany and other countries. It has led to the synthesis of a large number of compounds belonging to different types. The most important and useful of such antimalarial compounds belong to the following fundamental systems :

(*i*) quinoline; (*ii*) acridine and (*iii*) biguanide systems.

(*i*) *Quinoline derivatives.*—In 1926, the pharmaceutical department of I. G. Farben Industrie of Germany placed on the market a new synthetic antimalarial called *plasmoquin or plasmochin.* It is a quinoline derivative and has been assigned the structure :—(The official name is pamaquin).



Structurally, it is closely related to quinine, and is very efficacious as an anti-malarial. It consists of two parts: (1) the basic side-chain and (2) the quinoline residue ; hence its synthesis consists of the following:

(*a*) *Synthesis of the side-chain.*—This has been obtained in a number of ways. The steps involved in a few typical methods are :

(*i*) CH_2—CH_2 >O (ethylene oxide) + $NH(C_2H_5)_2$ $\xrightarrow{CH_3OH}$ CH_2OH—$CH_2N(C_2H_5)_2$

CH_2Cl—CH_2OH + $NH(C_2H_5)_2$ → CH_2OH—$CH_2N(C_2H_5)_2$

$\downarrow$ $SOCl_2$

(*ii*) CH_3—$CO{\cdot}CH_2{\cdot}COOC_2H_5$ + $ClCH_2$—CH_2—$N(C_2H_5)_2$

$\downarrow$ $NaOC_2H_5$

CH_3—$CO{\cdot}CH$—$COOC_2H_5$ (with CH_2—CH_2—$N(C_2H_5)_2$ on CH)

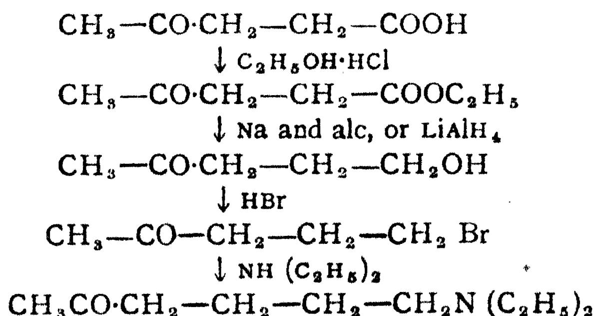
$\downarrow$ H_2O

CH_3—CO—CH_2—CH_2—CH_2—$N(C_2H_5)_2$

H_2,Ni / NH_3 ↙ ↘ oximation / reduction

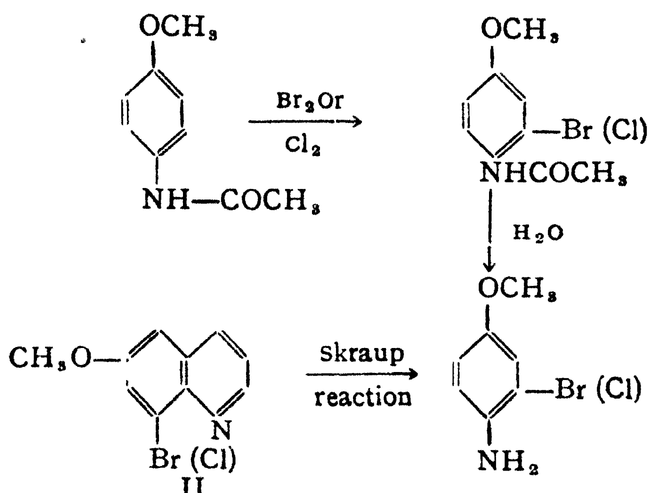
CH_3—CH—$(CH_2)_3$—N $(C_2H_5)_2$ (with NH_2 on CH) I

In another method, the starting-point is levulinic acid obtained by heating sucrose with HCl under pressure on a steam bath.

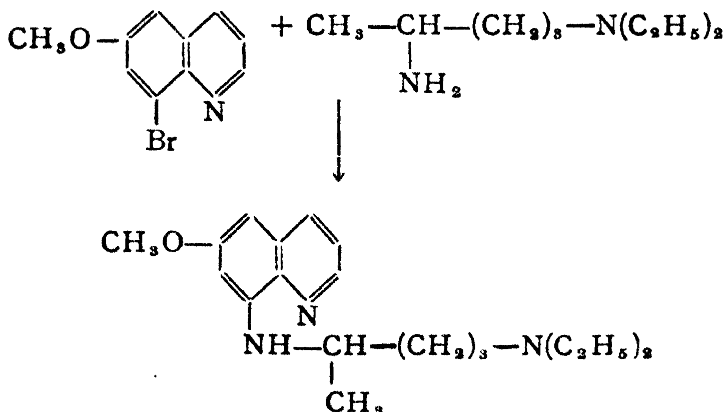


which is changed into I by one of the methods indicated earlier.

(*b*) *Synthesis of quinoline residue :*

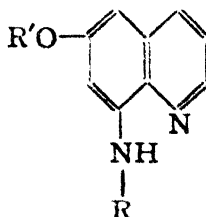


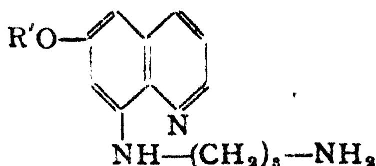
(*c*) *Synthesis of plasmoquin.*—The compound I is condensed with the compound II in amyl alcohol (under reflux) to give plasmoquin.



This discovery has led to systematic research on the synthesis of anti-malarials containing quinoline nucleus. Robinson and Barger have thus prepared a number of synthetic products possessing anti-malarial activity. Amino-alkyl-quinoline derivatives

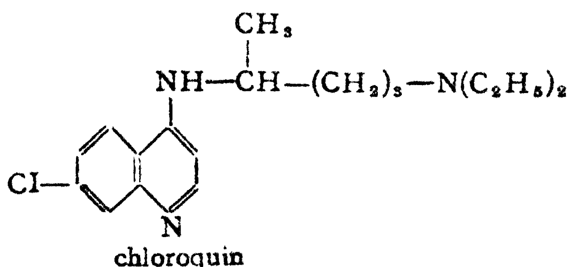
with the following structures have been prepared and found to possess anti-malarial activity :—



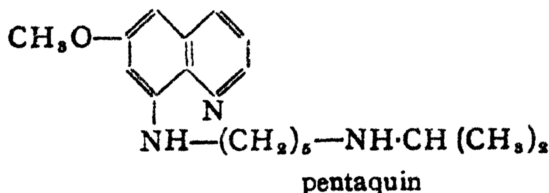


It is obvious that, such compounds are structurally very similar to plasmoquin.

But plasmoquin soon proved to be too toxic for general use and the I.A. announced in 1930, the preparation of a more successful anti-malarial—atabrine or atebrine, which contains an acridine system. During the last World War, two more anti-malarials belonging to the quinoline series have been developed. They are chloroquin and pentaquin.



chloroquin



pentaquin

Chloroquin is also referred to as the anti-malarial SN. 7618. Its manufacture on a large scale was undertaken in U.S.A. during the last World War. The rections involved may be expressed schematically as follows :

Cl—(benzene ring)—NH_2 + $COOC_2H_5$—CH_2—$CO{\cdot}COOC_2H_5$ ⟶ Cl—(benzene ring)—$N{=}C(COOC_2H_5)$—CH_2—$COOC_2H_5$

↓

(quinoline ring) OH, Cl—, —$COOC_2H_5$, N

⟵

(quinoline ring) OH, Cl—, N

↓ PCl_5

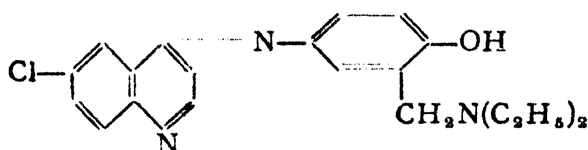
(quinoline ring) Cl, Cl—, N + CH_3—CH(NH_2)—$(CH_2)_3$—N $(C_2H_5)_5$

↓ C_6H_5OH

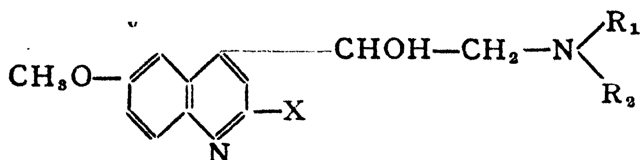
(quinoline ring) Cl—, N, —NH—CH(CH_3)—$(CH_2)_3$—$N(C_2H_5)_2$

chloroquin

The diphosphate is the drug. Another drug belonging to this group is camoquin and has the structure :

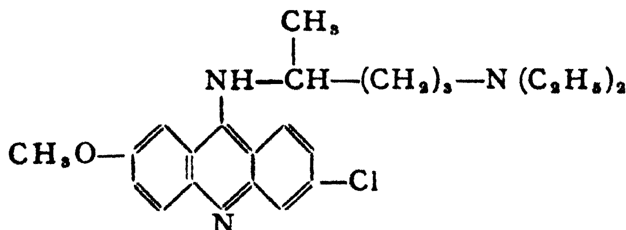


Recently, synthetic products based on the knowledge of the fate of quinine in the body, have been developed. They are 6-methoxy-quinolyl-carbinols of the general formula :



and are found to be active in bird malaria. It was found that in animals, quinine is oxidised in α-position in the quinoline nucleus to the corresponding hydroxy derivative. It was, therefore, suggested that the anti-malarial activity may be increased by prevention of the oxidation through introduction of an α-substituent in the quinoline ring. Many such compounds are prepared and some of them are found to be more active than quinine.

(ii) Acridine derivatives.—The most successful of the acridine derivatives as an anti-malarial is atabrine; it is also known by other names *e.g.* mepacrin and quinacrin. It has been assigned the structure:

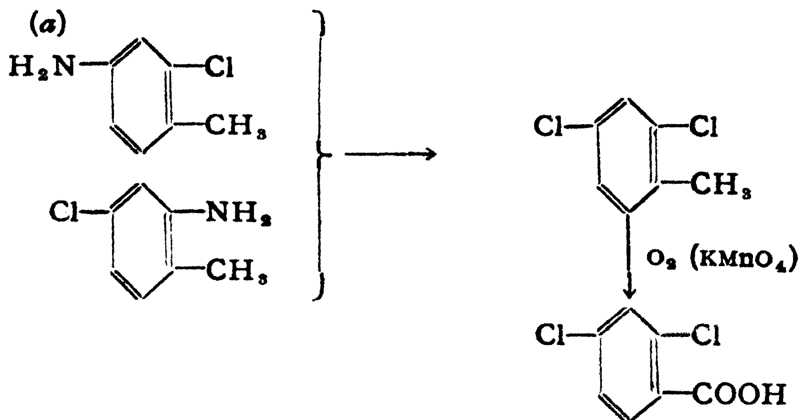


The preparation of atabrine was undertaken on a large-scale during the last war and consisted of three stages: (*i*) preparation of the side-chain; (*ii*) preparation of the acridine residue; (*iii*) condensation of I and II to give atabrine.

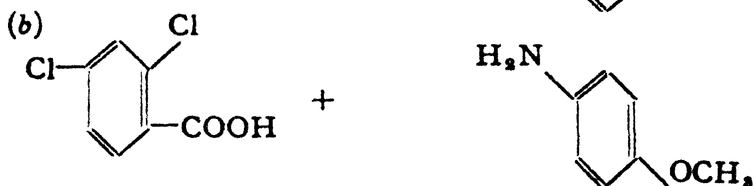
(*ii*) The side-chain is the same as is present in plasmoquin or chloroquin and, therefore, obtained by one of the methods discussed earlier.

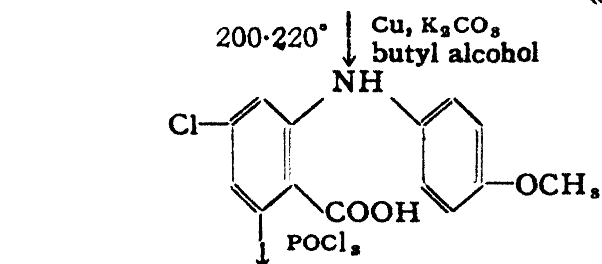
(*ii*) Preparation of the acridine residue; the steps involved are:

(*a*)



(*b*)





(*c*)

Cl

CH_3O—

—Cl

N

C_6H_5OH

$H_2—NCH—(CH_2)_3—N\ (C_2H_5)_2$

CH_3

$NH—CH—(CH_2)_3—N\ (C_2H_5)_2$

CH_3

CH_3O—

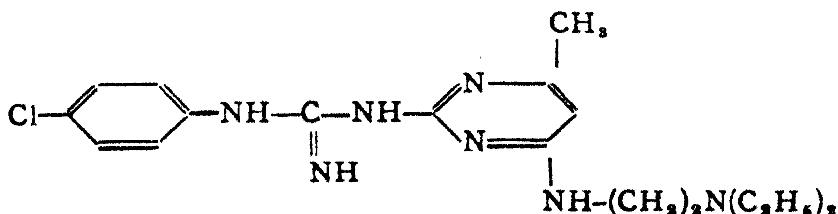
—Cl

N

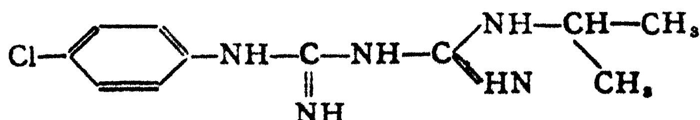
atabrine

The use of the drug, however, produces an objectionable yellow pigmentation of the skin and further does not prevent relapses, though it is a better suppressive than quinine. As atabrine was not very satisfactory, an intensive search for still better anti-malarials was carried out in the laboratories of the Allied Nations, during the war-time. Such research in England resulted in the development of a new drug which is a biguanidine derivative.

(*iii*) *Guanidine derivatives*—Curd, Rose and others in the hope of breaking away from the traditional heterocycles used in the synthesis of anti-malarials, turned to a new system—the pyrimidine system; this system is present in a large number of physiologically active natural products like vitamin B, folic acid and the nucleic acids. The sulpha drug—sulpha diazine which is found to be the most effective and least toxic of the sulpha drugs, contains a pyrimidine ring. They found the 2-aminopyrimidine derivatives to be sufficiently active; the activity was due to their capacity to exhibit tautomerism. This was followed by experiments with guanidino group in combination with the pyrimidine ring; p-chlorophenyl-2. (4 methyl-6-dimethyl amino-ethylamino-pyrimidyl) guanidine:

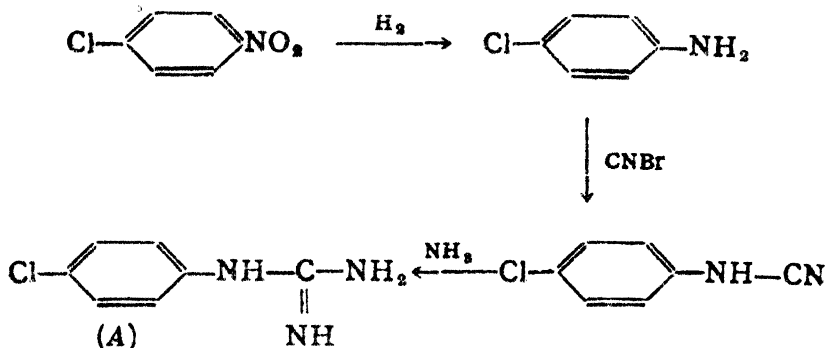


proved effective against *Plasmodium vivax*. From such a compound to biguanide is a short step; they are compounds in which the pyrimidine ring is opened up. A search in this direction finally led to the discovery of paludrine—a biguanide. It has the structure:

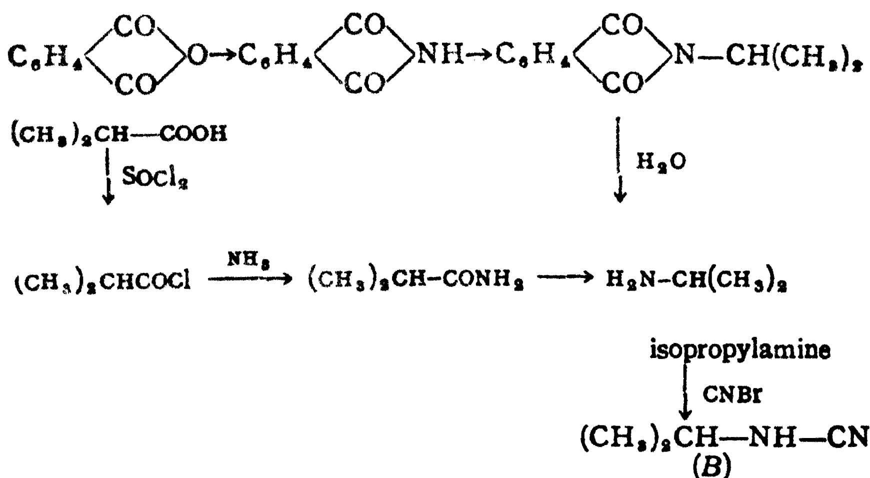


A synthesis of paludrine consists in condensing under suitable conditions, *p*-chloro-phenyl guanidine (A) and isopropyl cyanamide (B)

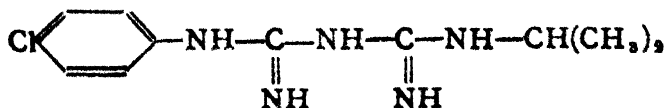
(*i*) *Synthesis of* (*A*):



(*ii*) *Synthesis of* (*B*):

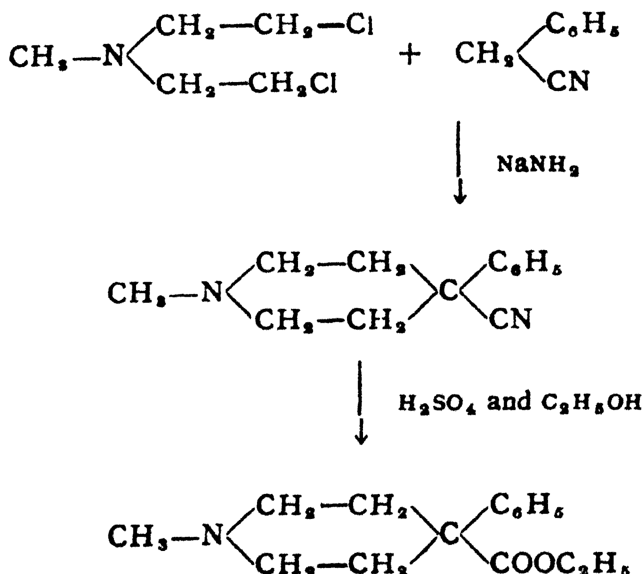


(*iii*) *Synthesis of paludrine*—A and B are fused together at 140.145° to give the biguanide : paludrine.



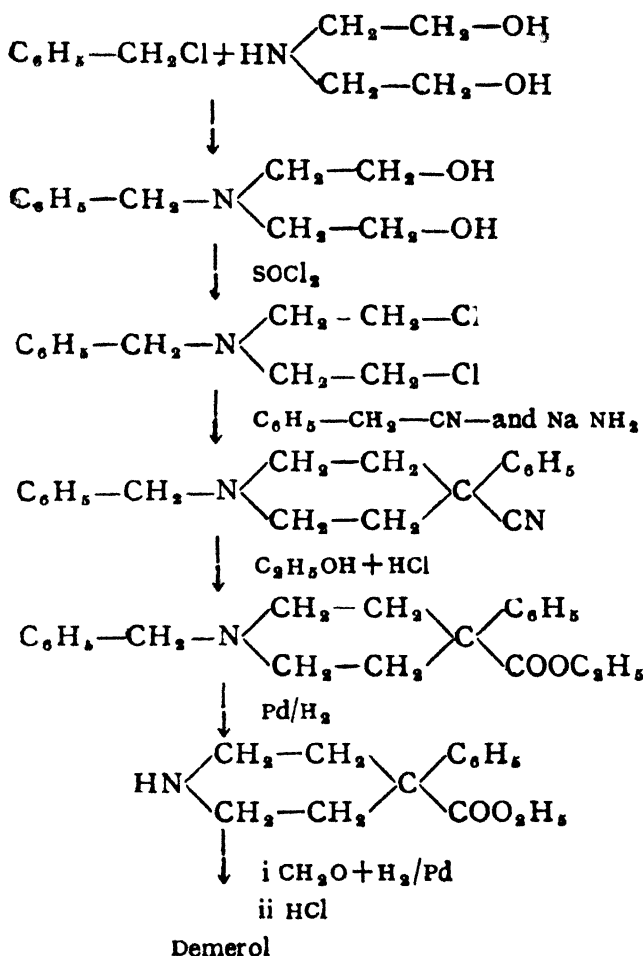
Paludrine has distinct advantages over atabrine; it is less toxic and does not cause the yellow pigmentation of the skin. It is also effective at a lower dosage. It is a suppressive for vivax malaria.

SUBSTITUTES FOR MORPHINE.—Development of substitutes for morphine has attracted the greatest attention of the organic chemist for a long time. It is a drug which is almost indispesable in medical practice as it is the most efficacious remedy for relieving physical pain. But it is a dangerous drug as it causes habituation and addiction. At first, a derivative of morphine like codeine was used extensively because of its relatively slight tendency to cause habituation. This was followed by a simple substitute called demerol, (meperidine or pethidine). It is a German product, and is much less toxic, but is less potent than morphine as an analgesic. It is obtained by the following series of reactions :

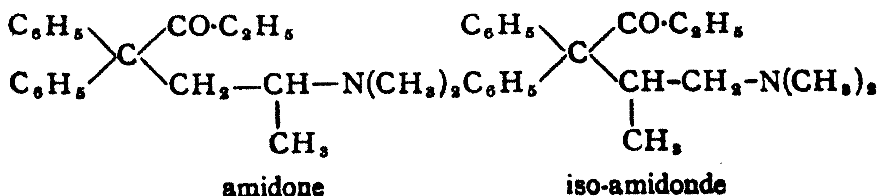


The hydrochloride of the above compound is the drug demerol.

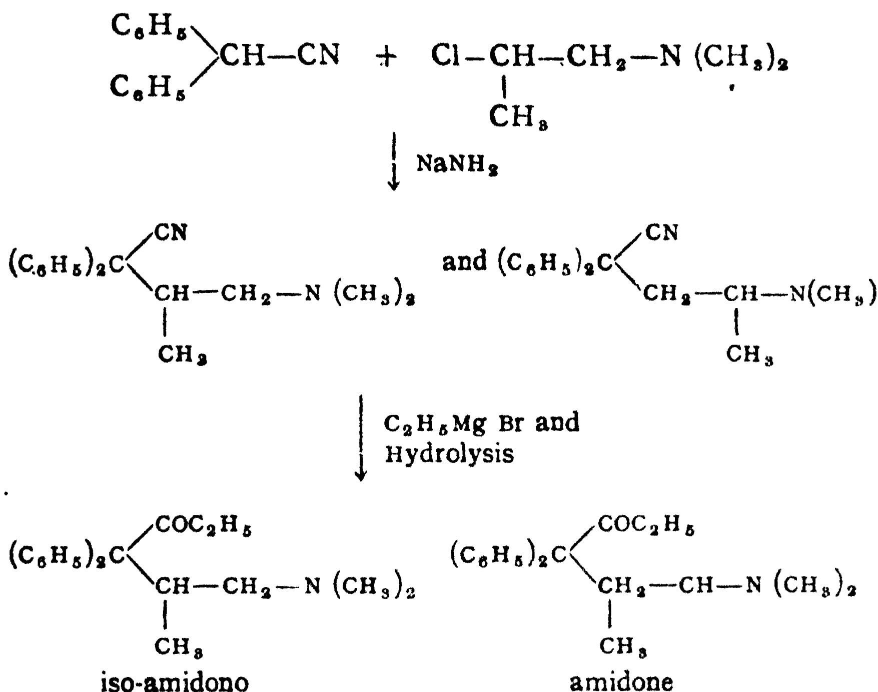
In a recent synthesis of demerol, the following reactions are employed. This avoids the use of the powerful vesicant as the starting-point.



Recently, two more drugs amidone and iso-amidone, with relatively simple structures have been introduced as substitutes for morphine. They have the structures :



They are as potent as morphine as analgesics and also possess less toxicity. But they are found to exhibit some undesirable side reactions. They are synthesised as follows :—



Amidone is the main product of the synthesis. A new synthesis from diphenyl aceto-nitrile and propylene oxide has been recently reported.

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